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ORIGINAL ARTICLES

EXPERIENCES GAINED IN A THIRTY YEAR STUDY OF PREMATURELY BORN INFANTS

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IF I were to discuss with you the general subject of the premature infant, I would probably bring you little that is new since most of us have gained similar results through our experiences. However, our greatest contribution lies in the fact that we are presenting a long range life history of our smallest graduates in a broad review of the results to date, leaving a more detailed description of the individual infants for future publication.

Much has been accomplished in our time in lowering mortality and morbidity among premature infants but it must be remembered that in these small infants, even with the best of nursing care and most modern equipment, the death rate cannot be cut beyond an irreducible minimum, largely because of their immature development at birth. I am sure it is obvious to all of us that, if we are going to reduce the number of premature deaths, our hope lies in the first week and especially in the first hours of life of these babies. In the general hospital this will require cooperation betwen the obstetrician, the pediatrician and the nursing supervisors of the two departments.

Our Premature Infant Station was started in 1922 with a capacity of eight cribs, the objective being to provide care for premature infants born in homes or in hospitals not equipped with the necessities for their complete care. The activities of the station have been made possible through the financial assistance and endowment of the Infants Aid Society of Chicago. This group of some 1000 philanthropically inclined women has furnished special equipment and layettes to our station, has founded and equipped a 12-crib-capacity station at the Mt. Sinai Hospital in Chicago, and has, through the years, furnished much in the way of layettes to the Premature Station at Cook County Hospital. The Sarah Morris Hospital Station was established as a memorial to the Society's first president, Hortense Schoen Joseph.

From the Sarah Morris Hospital of the Michael Reese Hospital, Chicago.

Borden Award Address read at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 22, 1952.

(Received for publication Oct. 24, 1952.)

FIG. 1. Eight premature infants in new nursery of Michael Reese Hospital. Ages range from 1 to 8 wk.; all weighed less than 1250 gm. at birth. (Exclusive *Sun-Times* photo by Dave Mann)

FIG. 2. Interior view of new nursery showing it to be compact unit with glass interior partitions so that supervisors may enforce aseptic technic.

FIG. 3. Floor plan of new nursery developed by Mr. John Black, architect of Michael Reese Hospital Planning Staff.

During the first three years of its existence, our Premature Infant Station with its eight cribs admitted only 94 infants due, in part, to the lack of enthusiasm with which the station was accepted by the medical profession in Chicago. Later its capacity was increased to 25 beds, and in 1951 a new unit was developed with capacity for 40 infants (Fig. 1). As might be expected, with a background of years of experience in the care of the premature infant, changes have developed in technics and physical lay-out in such a unit, some of which might be of interest to you. For instance, the hospital has eliminated the requirements for nurses and other personnel in the station to wear masks, while physicians and others who must be in the nursery for only short periods of time are usually required to wear masks. Also, on the basis of experience in our station, it is believed that the standards of the United State Public Health Service for at least 24 and preferably 30 square feet of space per bassinet are needlessly large and that there is a definite operating advantage in the restriction of space per bassinet. The new unit, therefore, has 40 bassinets with a net floor space of 18 square feet per bassinet, which allows for more adequate, detailed supervision from a central control point (Figs. 2 and 3).[1]

CHART 1

PREMATURE INFANT STATION STATISTICS FROM 1922 TO JANUARY 1, 1952

Wt. (gm.)	Total	Graduated	Per cent graduated	Fatality Rate in Station			
				Under 24 hr.	24–28 hr.	48–72 hr.	Over 72 hr.
Less than 1,000	759	99	13.0	448	74	69	69
1,001–1,250	834	346	41.5	283	84	63	58
1,251–1,500	1,410	926	65.7	263	77	86	58
1,501–2,000	3,549	2,936	82.7	296	93	170	54
2,001–2,500	2,470	2,240	90.7	103	42	77	8
Totals	9,022	6,547	72.6	1,393	370	465	247

Note: Excluding 24 hr. deaths, 85.8+% survived.
Excluding 48 hr. deaths, 90.2% survived.

Chart 1 bears out my previous statement that it is the first few hours of life of these small infants that are so important if we are to reduce our mortality and morbidity statistics.

Many of these babies were received late and in poor condition but, by regulation of the Chicago Board of Health, any infant showing signs of life when received in the station must be included in the statistics. In the total group of 9022 infants admitted to the station are included 759 whose birth weights ranged from 605 gm. (Fig. 4) to 1000 gm.; 99 (13.0%) of these smallest infants were graduated from the station and the time of death of the remaining 660 was as follows:

First 24 hours—448
24 to 48 hours— 74
48 to 72 hours— 69
After 72 hours— 69

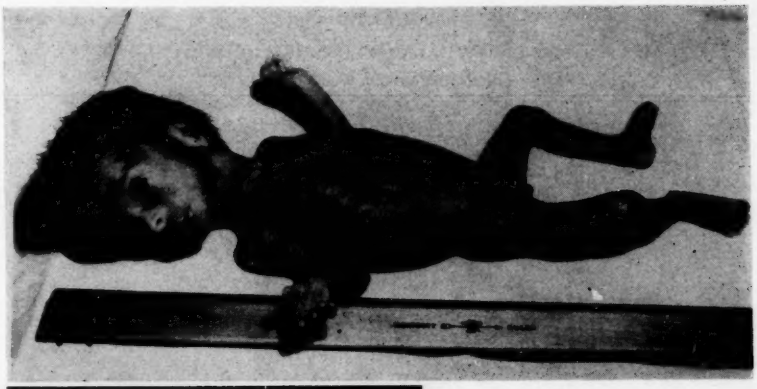


FIG. 4. P. P., our smallest living graduate, born 12/4/48; birth weight 605 gm., low weight 500 gm. B: P. P. at 3½ yr. of age.

In the next birth-weight group, 1001 to 1250 gms., 834 infants were admitted to and 346 (or 41.5%) were graduated from the station. Death of the remaining 488 occurred as follows:

First 24 hours—283
24 to 48 hours— 84
48 to 72 hours— 63
After 72 hours— 58

Further study of chart 1 reveals that 99 infants graduated whose birth weights were less than 1000 gm. and 346 infants graduated whose birth weights were between 1001 and 1250 gm. It is this group of 445 prematurely born infants with birth weights of

CHART 2

445 PREMATURE INFANTS GRADUATED FROM 1922 TO JANUARY 1, 1952
(Birth weights 605 to 1,250 gm.)

Living	370
Deceased	45
Not available	30
Total	445

Present age of those with birth weight below 1,000 gm.

22 yr. or over	3
15 to 22 yr.	14
10 to 15 yr.	14
8 to 10 yr.	15
5 to 8 yr.	18
2 to 5 yr.	17
Less than 1 to 2 yr.	18
	99

1250 gm. or less about which I wish to devote most of my remarks today. The 1250 gm. weight as the upper limit for the group of smallest infants was selected arbitrarily for this report. In a 1949 report we included 20 infants with birth weights between 1250 and 1260 gm. but to simplify a comparison of results obtained in other clinics we are now dividing the birth weights into groups of 250 gm.

One frequently reads in the public press of the birth of one of these small infants and occasionally its early progress is reported but usually its ultimate development is left to the imagination. This, together with the fact that we must all answer the question of whether these very small premature infants are worth saving, encouraged us to believe that a long range study of our smallest babies would be of instructive interest. We are, therefore, presenting the life history of these infants with as true an estimation as possible of their physical growth and mental development.

Of these 445 smallest infants, 370 are still living and are known to us; their ages

CHART 3

ESTIMATED DEVELOPMENTAL RATINGS OF 370 CASES
(Birth weight up to 1,250 gm.)

Physical Development	Rating	Mental Development
200	IV	264
116	III	68
36	II	23
13	I	6
5	0	9

Rating IV—normal average, some superior
Rating III—slight deviation based on expectation for age
Rating II—poor
Rating I—bad
Rating 0—extremely subnormal

CHART 4

SURVIVORS OF INTRACRANIAL PATHOLOGY DIAGNOSED IN PREMATURE STATION

Suspected cases in station	88
No present evidence of pathology	47
Pathology present at last examination	41*
Cerebral palsy, normal mentality	23
Cerebral palsy, deficient mentality	6
Pure mental deficients without spasticity	12

* Included are:
3 cases of 21 cases of retrolental fibroplasia reported
1 living case of Tay-Saks disease
3 cases of cerebral agenesis

range from somewhat less than one to over 28 years, and 335 of them were brought to us for personal interview and photograph and many of them for repeated examination and study; 35, located in distant cities, were examined by their own pediatrician or family doctor who transmitted to us reports of their mental and physical development. Of the remaining 75, we have positive knowledge of 45 deaths but we have been unable up to the present time to obtain positive information concerning the last 30, some of whom may have died. The results of this study are presented in the charts 2 to 8.

Chart 6 is of particular interest to us for two reasons: (1) For many years it was our custom to give blood intramuscularly at least once to all small premature infants in an effort to increase their antibody production and to improve their nutritional status. However, in recent years it has been suggested that such blood administration would result in Rh-negative blood with resultant erythroblastosis. This has not been verified so far as the married females in our series are concerned. (2) Over the years there has been definite skepticism in the minds of some as to the ability of these small infants, first, to become pregnant, and second, to deliver full-term children. Our statistics show that of the 14 graduates who have married (Fig. 5), 10 have been delivered of 12 living children; in only one instance was there a stillborn reported and this graduate later was delivered of a full term baby.

At the Michael Reese Hospital an outpatient clinic is maintained for instruction of mothers of premature infants and for the care and supervision of graduates from the

CHART 5

INTRAOCULAR PATHOLOGY

Retrolental fibroplasia		21
Unilateral (none spastic)	8	
Bilateral	13	
With spasticity	3	
Without spasticity	10	
Cataracts		6
Unilateral (2 operated)	5	
Bilateral	1	
Miscellaneous pathology		2
Microcornea with optic nerve pathology	1	
Choroiditis	1	

CHART 6

MARRIED GRADUATES

Female—11
Male — 3

Initials	Case No.	Sex	Birth wt. (gm.)	Present age (yr.)	No. and age of living children
I.V.	187	F	935	26	1st—3 yr.; 2nd—1 yr.
R.D.	160	F	935	20	0 (retrolental fibroplasia)
R.F.	2	F	995	20	1—1 yr.
M.B.	33	F	1,000	17	1—newborn
A.J.	106	F—	1,060	27	1—2 yr.
B.W.	102	F	1,075	28	1 (cesarean section)
D.P.	36	F	1,075	24	0
E.N.	91	F	1,090	26	1st—stillborn at 8 mo.; 2nd—3 yr.
D.R.	56	F	1,110	24	1—2 yr.
M.S.	183	F	1,245	24	1—1 yr.
M.N.	65	F	1,250	23	0
W.M.	47	M	1,150	27	1—1 yr.
R.G.	148	M	1,240	25	0
L.P.	213	M	1,130	28	1st—3 yr.; 2nd—18 mo.

CHART 7

GRADUATES WHO SERVED IN ARMED FORCES DURING WORLD WAR II

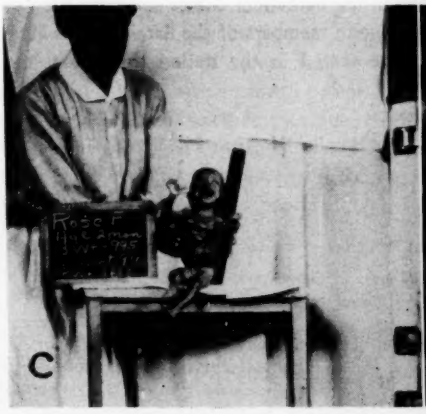
W.M. Case No. 47—Served in Army
Birth wt. 1,150 gm.
Present age 27 yr.
R.G. Case No. 148—Served in Army
Birth wt. 1,240 gm.
Present age 25 yr.
L.P. Case No. 213—Serve in Navy
Birth wt. 1,130 gm.
Present age 28 yr.

CHART 8

PREMATURE INFANT OUTPATIENT CLINIC, MICHAEL REESE HOSPITAL

Year	1946	1947	1948	1949	1950	1951
New cases	111	101	135	145	130	149
Individuals	359	408	376	450	431	503
Total visits	1,315	1,576	1,827	2,644	2,510	2,525

FIG. 5 (see chart 6). Two of nursery's smallest premature infants who have married. A: R. D. at 35 days of age; birth weight 935 gm., low weight 850 gm.; B: R. D. at 20 yr. of age. C: R. F. at 2 mo. of age; birth weight 995 gm., low weight 910 gm.; D: R. F. at 21 yr. of age with her son, 6 mo. of age.



station. This clinic was established so that the many patients who come from families in the lower income bracket and who frequently do not have private physicians may still have access to guidance in the care of these infants.

I spoke earlier of the fact that some changes have been made recently in the technics used in our new station but I think emphasis should be placed on one practice that has not changed: We are just as firmly of the opinion now as we were in 1922 that breast milk is essential to the welfare of these small prematurely born infants. The mothers of the babies who are patients in the station express their milk at home and send it to the hospital to be used or, if this is not possible, breast milk is obtained from wet nurses and visiting mothers. More than 50% of the breast milk used for our small infants is obtained from mothers who have infants in the station. Except in cases where the mother still has ample breast milk at the time of discharge of the infant, the babies are started on a formula during their last days in the station.

In summary, I would point out that 445 infants weighing 1250 gm. or less at birth have been graduated from our Premature Infant Station during the past 30 years and that approximately 83% are known to us to be still living; that 85% of these living graduates are of average or above average physical development and 90% are of average or above average mental development; three of the young men served with credit in the Armed Forces of our country during World War II, and the 14 married graduates have to date furnished 12 living children to the next generation. I give you these statistics in support of our original belief that any effort expended in the care of these smallest prematurely born infants is of inestimable value. Nature has been kind to many who did not survive the ordeals of the early days, but it is hoped that with further progress in their care there will result not only continued lowering of early mortality but improved physical growth and mental development of the prematurely born infant.

It must be evident to all that in order to present such a report as has been given today, many individuals must have been interested in the welfare of these children. Special mention should be made of Evelyn Lundeen's 28 years as Head of the Premature Infant Station, Roberta Stannard's 22 years as Head of the Field Service and Outpatient Clinic, and Winifred Witz's 14 years as second-in-charge of the Station. Many members of the Infants Aid Society have served for long periods in the outpatient clinics and have been of further help in the field services. Credit is also due to members of the Sarah Morris Hospital pediatric staff and resident staff who have served in the station throughout the years.

REFERENCE

1. Black, J. T., New premature nursery at Michael Reese Hospital, Hospitals **26**:83, 1952.

104 South Michigan Avenue

NITROGEN UTILIZATION IN CALORIC INSUFFICIENCY

By WARREN M. COX, JR., PH.D., RUDOLPH C. ELLINGSON, PH.D., AND A. J. MUELLER, B.S.

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THE protein requirement and factors determining the efficient utilization of protein for tissue synthesis have engaged the attention of many biochemists and clinicians. A few of the many factors influencing protein utilization are the amount of protein in the diet, the need for protein, the relative amount of fat and carbohydrate in the diet, the time of ingestion of protein relative to the ingestion of other foodstuffs, the biologic value of the ingested protein, any stress to which the organism is subjected, and the relative sufficiency of calories to meet energy requirements.

The importance of calories in improving the efficiency of protein utilization was observed by Rubner in 1883[1] and subsequently has been too often confirmed to require documentation. Protein can be used either for tissue synthesis, or for calories, and this dual role emphasizes the importance of supplying adequate fat or carbohydrate if protein is not to be used, in part, to meet basal energy needs. Maximal utilization of protein for tissue synthesis is dependent on supplying sufficient calories for all energy requirements. From this it has been held that protein cannot be used for tissue synthesis unless the energy requirements are fully supplied,[2] that the caloric requirements have priority over the protein requirements,[3] and that ingested protein will be catabolized for energy if the basal needs for energy are not first met.[4]

Contrary to these beliefs are the findings of Allison et al.,[5] Bosshardt et al.,[6] Swanson,[7] Benditt et al.[8] and Elman et al.[9] and others who have shown that a portion of ingested protein is utilized for tissue synthesis, or for gain in weight, or to promote nitrogen equilibrium even when the caloric intake is restricted to less than total energy requirements. The emphasis of their reports, however, was that maximal utilization is accomplished only if sufficient calories are supplied.

The purpose of this study was to determine to what extent ingested protein can be used for tissue growth when insufficient calories are fed. Since the demonstration of growth in animals with a growth potential is a measure of tissue synthesis, young rats were used to determine whether the requirement for calories takes precedence over the requirement for tissue growth. It was a further object of this work to determine whether there is a particular proportion of protein to carbohydrate that can be used most effectively when the calorie supply is suboptimal.

EXPERIMENTAL

Animals with differing nutritional reserves were prepared by treating 100 gm. rats (inbred Wisconsin strain) in 4 different ways. One group was fed a protein-free diet* *ad libitum* for 2 wk.

From the Mead Johnson Research Laboratories, Evansville, Ind.

Presented at the meeting of the American Pediatric Society, Old Point Comfort, Va., May 7-9, 1952.

(Received for publication Sept. 11, 1952.)

* The composition of the protein-free diet was as follows: dextrose 92.3%, corn oil 1.0%, agar 2.0%, salt mixture 4.0%, vitamin mixture .7%, oleum percomorphum .02%.

TABLE 1

COMPOSITION OF DIETS

Each animal was fed daily the indicated quantities. Dextrose 1 gm. supplied 3.8 cal.; protein hydrolysate 1 gm., 3.7 cal.

	Dextrose Diets				
Calories as dextrose	10	15	20	30	50
Calories as fat	1	1	1	1	1
Vitamin mixture (gm.)	.07	.07	.07	.07	.07
Mineral mixture (gm.)	.40	.40	.40	.40	.40
Oleum percomorphum (gm.)	.002	.002	.002	.002	.002
Agar (gm.)	.20	.20	.20	.20	.20
	Dextrose—Protein Hydrolysate				
Calories as dextrose	5	10	15	25	45
Calories as protein hydrolysate	5	5	5	5	5
Calories as fat	1	1	1	1	1
Vitamin mixture (gm.)	.07	.07	.07	.07	.07
Mineral mixture (gm.)	.34	.34	.34	.34	.34
Oleum percomorphum (gm.)	.002	.002	.002	.002	.002
Agar (gm.)	.20	.20	.20	.20	.20

One group was partially starved by feeding 20 to 22 cal. daily of a nutritionally adequate, synthetic diet containing casein hydrolysate, so that weight was stationary. The other 2 groups were allowed stock food *ad libitum* and half of these animals then scalded by immersion for 5 sec. in water at 65° C.

Groups of 6 animals, prepared as described above and equally divided as to sex and litter were fed isocaloric quantities of dextrose and of dextrose and protein hydrolysate (amigen®) for 5 wk. periods. The 5 diets supplied 11, 16, 21, 31 or 51 cal. daily and agar 0.2 gm., oleum percomorphum .002 gm., vitamin mixture 0.7 gm. and salt mixture .40 (or .34) gm. Composition of diets is given in table 1. Composition of the vitamin mixture, in per cent, was as follows: thiamine hydrochloride .029, riboflavin .044, niacinamide .733, calcium pantothenate .293, pyridoxine HCl .037, folic acid .029, menadione .029, biotin .003, para-aminobenzoic acid 1.466, inositol 14.659, choline bitartrate 29.318, APF supplement supplying 27.5γB_{12} activity/gm. 53.359. Salt mixture was U.S.P. salt mixture No. 2 with the 4 trace minerals in U.S.P. salt mixture No. 1 added. Less salt was added to the diets containing casein hydrolysate because of salts present in the hydrolysate.

Animals were housed individually in wire-bottomed cages in a room held at a temperature of $24 \pm 2°$ C. They were fed daily, and record made of any food remaining in cups the next morning. Rations containing hydrolysate were consumed completely save for the 51 cal. diet which was in excess of requirements. Intake on this diet was essentially *ad libitum* and was considered as approximating optimal energy intake. Dextrose alone was not accepted well, and record was kept of the amount consumed. Eleven and 16 cal. as dextrose were completely consumed, but when more was offered, consumption varied between 17 and 28 cal.

To estimate basal energy requirements the authors have used the formula and standards applied usually to well-nourished stock animals, i.e., Rubner's formula for surface area, $S = 9.1 \times W^{\frac{2}{3}}$, and a value of 1050 cal. as the basal energy requirement/m^2.[10] These assumptions give the basal-energy requirement of well-nourished 100 gm. animals as 20.6 cal. Because it is difficult to estimate the minimal energy requirement of these animals that have been scalded, protein-depleted or partially starved, and since the energy required for growth, activity and specific dynamic action must be added to the basal requirements, the authors have chosen 30 cal. daily as a value that approximately expresses the minimal energy requirement.

After 5 wk. the animals were killed, gastrointestinal tract removed, carcasses placed in individual pint jars and autoclaved for 4 hr. at 15 lb. steam pressure. This period of autoclaving facilitates the making of a uniform paste of the carcass in a Waring blendor. Analysis for nitrogen was by Kjeldahl method,[11] fat and total solids by the procedure described by Sarett and Jandorf, slightly modified,[12] for ash by incineration of the fat-free, dried tissue at 550° C.

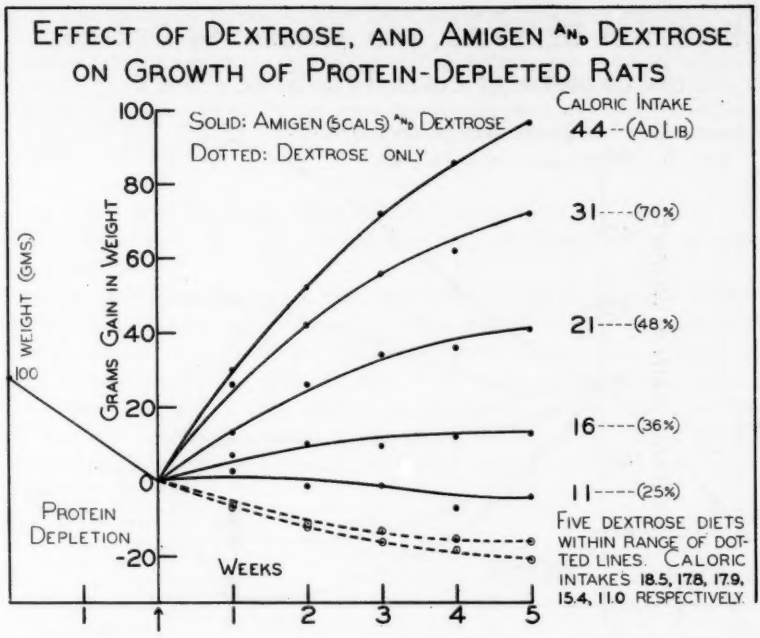

CHART 1. Gain in weight of protein-depleted animals fed dextrose or dextrose and protein hydrolysate (amigen®) in adequate and less than adequate quantities to meet energy requirements.

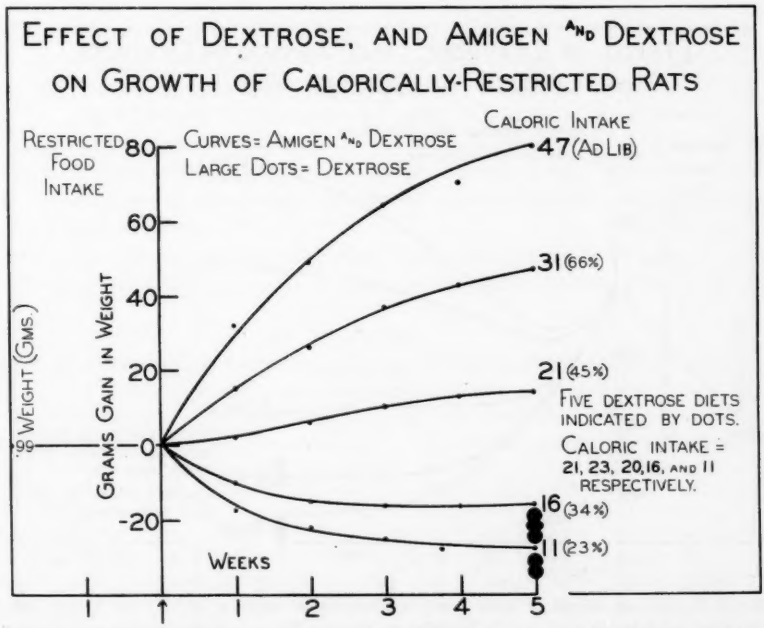

CHART 2. Gain in weight of young rats restricted in calories for a period of 2 wk., and then fed dextrose or dextrose and protein hydrolysate (amigen®) in adequate and less than adequate quantities to meet energy requirements.

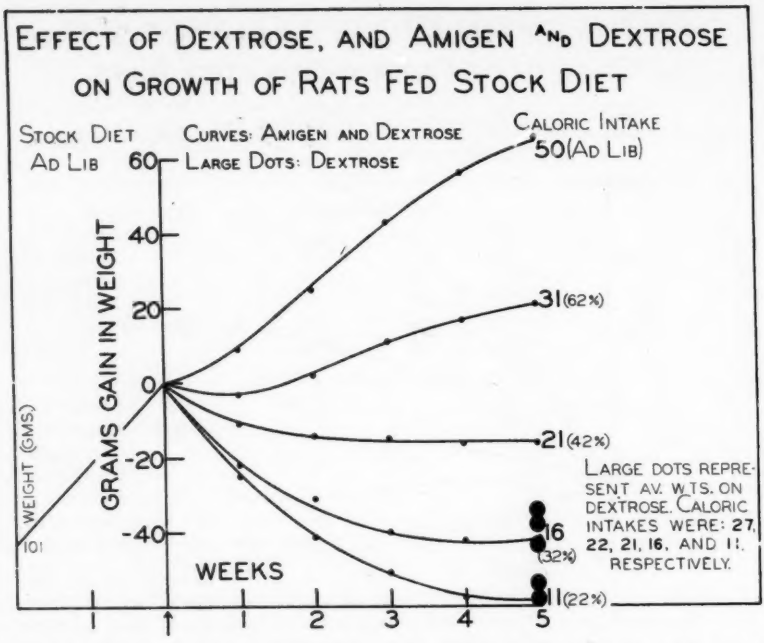

CHART 3. Gain in weight of 100 gm. stock rats permitted to grow on stock diet for 2 wk. and then fed dextrose or dextrose and protein hydrolysate (amigen®) in adequate and less than adequate quantities to meet energy requirements.

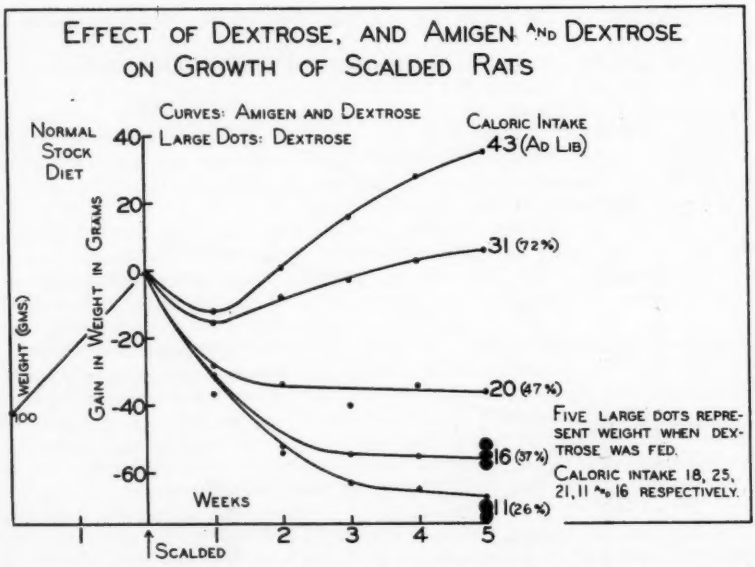

CHART 4. Gain in weight of stock rats after scalding in water at 65° C. for 5 sec., and then fed dextrose or dextrose and protein hydrolysate (amigen®) in adequate and less than adequate quantities to meet energy requirements.

In another series of experiments, the authors studied the best ratio of protein hydrolysate to dextrose at a 20 cal. level by varying the proportions of hydrolysate and glucose. Diets of the composition outlined above supplied 20 cal. in the following proportions of hydrolysate to dextrose—0:20; 4:16; 8:12; 12:8; 16:4; 20:0. The animals were fed for 5 wk. and changes in weight, water intake and mortality noted.

Results

Charts 1 to 4 show the weight changes of the four groups of animals having different nutritional status when they were fed isocaloric levels of dextrose and of dextrose and protein hydrolysate.

Protein-depleted Rats: During the two week protein depletion period the animals lost approximately 30 gm. in weight (chart 1). When offered *ad libitum* quantities of the dextrose-hydrolysate diet (51 calories), the rats ingested 44 calories and gained weight rapidly. As shown by the solid lines in chart 1 restriction in growth resulted from restriction in calories to 31 and 21 daily. There was slight growth when 16 calories was fed and weight maintenance with 11 calories. Eleven calories is 25% of *ad libitum* intake—the quantity teleologically required to meet the energy and protein requirements of these animals.

TABLE 2

Calories Ingested by Rats Receiving Dextrose Diets

Calories offered	11	16	21	31	51
Protein-depleted	11.0	15.4	17.9	17.8	18.5
Calorie-restricted	11.0	16.0	19.5	23.0	20.7
Scalded	10.9	15.9	20.8	25.0	17.5
Stock	11.0	16.0	20.7	21.9	26.5

Weight changes when dextrose only was offered are shown by the dotted lines in the chart; all five diets fell between the two curves. The 11 and 16 calorie portions were completely consumed, and when larger quantities were offered (i.e., 21, 31 and 51 calories) 17.9, 17.8 and 18.5 calories were eaten. It may be of some interest to note that the protein-depleted animals ingested less of the dextrose diet when it was offered in quantities adequate for energy needs than did the animals in the other three nutritional states. A tabulation of the amount of dextrose calories ingested, compared with that offered, is given in table 2.

These data on food consumption indicate that to strictly compare the animals receiving a nonprotein diet with those receiving dextrose and protein hydrolysate only the lowest

TABLE 3

Summary of Average Weight of Rats after 5 Weeks of Feeding Indicated Diets

(small superscript numbers indicate number of deaths)

Nutritional Status	Dextrose Diets					Dextrose and Protein Hydrolysate Diets				
Calories offered	11	16	21	31	51	11	16	21	31	51
Protein-depleted	54.3	49.7	56.5	55.3	56.7	66.3	83.7	111.5	142.2	167.2
Caloric-restricted	64.1[1]	68.0	77.8	79.7	78.2	69.5[1]	84.2	112.8	146.5	178.3
Scalded	69.8[2]	72.5[1]	83.8	88.2	87.2	74.4[1]	86.5[1]	109.9[2]	147.0[2]	177.2[1]
Stock	81.5	83.5	104.2	107.7	104.7	82.7	96.8	133.0	167.3	212.5

three calorie levels (or lowest two levels in the protein-depleted group) can be used. Animals receiving 11 calories as dextrose-hydrolysate weighed at the end of the five week period 12 gm. more than those receiving 11 calories as dextrose (table 3). The difference (because of the small variability in these underfed animals) is statistically significant, with a "t" value[13] of 7.8.

Calorically-Restricted Animals: Chart 2 presents the same type of findings for young animals held stationary in weight for two weeks by feeding only 20 to 22 calories daily and then given the same diets as in the above group. The nutritional deficiency is not as severe as in protein depletion because there was no pre-existing weight loss, and the weight response to feeding was less. The weight response to dextrose was inferior to isocaloric quantities of dextrose and hydrolysate at all levels.

Stock Animals: In chart 3 are the weight curves of animals with no pre-existing nutritional stress when subjected to the described dietary regimen. In these animals caloric deprivation restricted growth more than in the protein-depleted and calorically restricted animals. No growth occurred when the caloric intake was restricted to 50% of *ad libitum* intake. At 11 calories there was no advantage in supplying the nitrogen supplement, and at 16 calories any advantage was quite small. No comparisons were possible at higher caloric intakes for reasons previously mentioned. Apparently stock animals have a dispensable store of fat and protein that is rapidly lost in response to caloric restriction.

Scalded Animals: Recovery from the trauma of scalding requires about one week even when adequate calories and nitrogen are supplied (chart 4). Caloric restriction to 70% of the diet supplying nitrogen resulted in weight maintenance; and more severe restriction to weight loss. However, as shown in chart 4, even when the caloric restriction is as

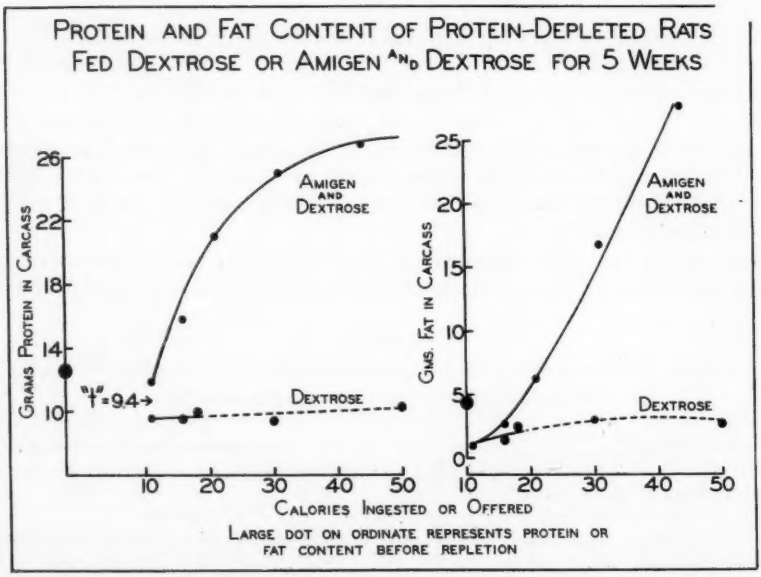

CHART 5. Protein and fat contents of animals whose gains in weight are shown in chart 1. Snedecor's "t" value is calculated for carcass-protein contents at 11 cal. intake.

TABLE 4

CARCASS ANALYSES: AVERAGE GRAMS PROTEIN AND FAT AND PER CENT SOLIDS IN CARCASSES OF ANIMALS FED DIETS CONTAINING DEXTROSE AND DEXTROSE AND PROTEIN HYDROLYSATE

Nutritional Status	Dextrose					Dextrose and Protein Hydrolysate				
Calories offered	11	16	21	31	51	11	16	21	31	51
	Gm. Protein, Average/Animal									
Protein-depleted	9.4	8.8	10.0	9.6	10.3	11.9	15.7	21.0	25.0	27.0
Calorie-restricted	12.6	13.6	15.3	15.6	15.6	13.2	17.2	22.4	28.1	29.8
Scalded	14.2	14.5	17.0	16.9	16.6	14.9	17.9	21.7	28.1	32.1
Stock	16.2	17.0	20.1	19.6	18.9	16.3	19.2	27.2	31.9	36.5
	Gm. Fat, Average/Animal									
Protein-depleted	1.1	1.4	2.6	3.0	2.7	1.0	2.7	5.4	16.8	27.7
Calorie-restricted	1.1	2.7	5.1	6.0	5.0	1.0	2.1	7.2	14.3	31.2
Scalded	.7	1.8	3.2	6.0	6.0	.8	1.5	3.6	11.8	21.0
Stock	1.3	2.9	7.6	11.0	10.0	1.1	1.9	6.7	18.3	42.7
	Per Cent Solids, Average									
Protein-depleted	30.2	29.1	32.0	32.2	32.7	30.6	30.5	31.6	37.1	40.5
Calorie-restricted	31.8	32.9	35.0	35.3	34.5	31.6	31.4	34.1	35.6	41.5
Scalded	31.0	32.8	32.7	34.9	34.4	31.6	31.5	31.8	35.1	37.3
Stock	32.4	31.5	35.5	37.0	36.9	32.1	31.0	33.4	37.0	44.4

Stock rats from colony were killed and carcasses analyzed as above for fat, protein and per cent solids. Six animals weighing an average of 196.3 gm. and 6 rats weighing 93.8 gm. were chosen. Weight, in grams of protein and fat, and per cent total solids, were, respectively, 35.1, 20.8, 35.3, and 14.7, 7.3 and 31.7.

much as 47% of *ad libitum,* the weight of the scalded animals is maintained better if they are given a source of nitrogen, than if they are given dextrose only.

Weights and Carcass Analysis: The average weights for all animals at the end of the experiment are given in table 3. Irrespective of caloric level, or of previous nutritional status, the animals receiving the hydrolysate weighed more than those receiving dextrose only. These findings are confirmed by carcass analyses (chart 5 and table 4) which show that the hydrolysate-fed animals have a higher body protein content for each caloric level, irrespective of nutritional status, than do the dextrose-fed animals. There is no significant difference in the amount of fat in the carcasses at the lower caloric levels, but at 21 calories and higher, the hydrolysate animals contain more fat than comparable animals on dextrose. The total solids in the carcasses indicate that the observed weight changes were valid and are not due to water retention. At the lower caloric intakes there are no significant differences between total solids—irrespective of feeding or nutritional status. The expected solids content for normal animals is observed in the group of stock animals fed 31 calories. The high solids at the 51 caloric level (37 to 44%) is attributed to fat deposition.

Water Requirement: Protein increases the renal excretory load and it has been repeatedly shown that the water requirement increases with and is proportional to the protein intake. Chart 6 illustrates the average daily water intake of the protein-depleted animals. Water intake is greater when the dextrose-hydrolysate diet is fed, and increases with caloric intake, even though the nitrogen intake is constant. Since more urea should

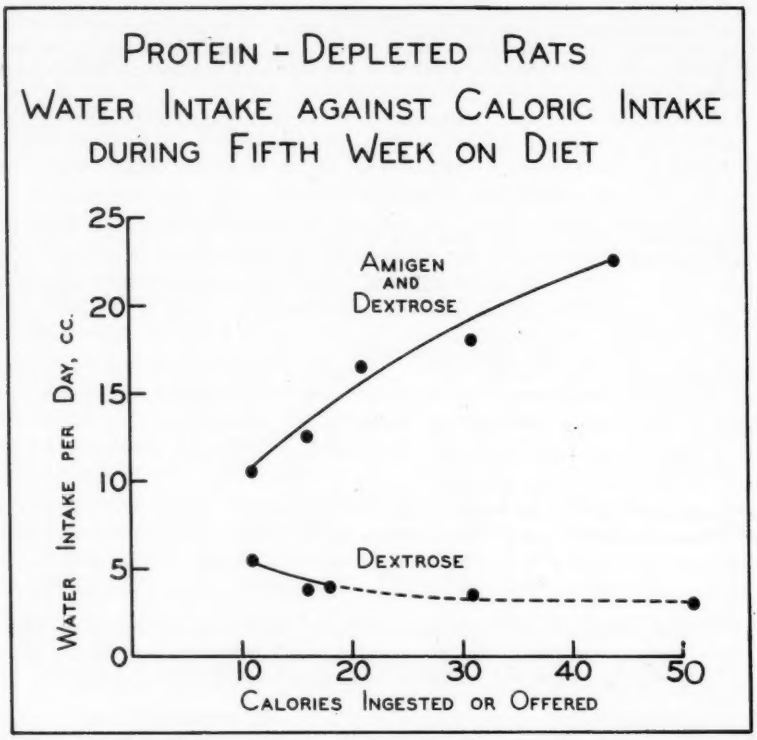

CHART 6. Water intake of protein-depleted animals receiving or offered isocaloric quantities of dextrose or of dextrose and protein hydrolysate (amigen®).

be excreted on the low calorie intake, the increase in water intake with increase in calories cannot be attributed to increase in excretory load, but probably to an increase in insensible water loss as the animal grows and becomes larger.

Protein Efficiency: Protein can be used either for tissue growth or for energy, depending in part on the total caloric intake and the nutritional needs of the organism. This is illustrated in chart 7, which shows that (a) the most efficient use of protein for growth occurs at the highest caloric intake and (b) growth (and tissue synthesis) also may occur at lower caloric levels. The horizontal line in the chart, at 30 calories, is drawn to represent the approximate energy requirement. Values to the right of the zero point, and below the horizontal line, indicate tissue growth with caloric insufficiency. The three parallel lines in the figure are displaced to the right or left depending on the degree of protein deprivation. Displacement to the right indicates greater tissue need, and shows that new tissue can be synthesized even though the caloric restriction is severe. This is best shown in the protein-depleted animals. The displacement of the line to the left indicates but little ability to synthesize new tissue when the caloric intake is restricted. This is true of the stock animals. The partially starved animals are intermediate.

Protein:Carbohydrate Ratio: In chart 8 are shown the weight changes of protein-

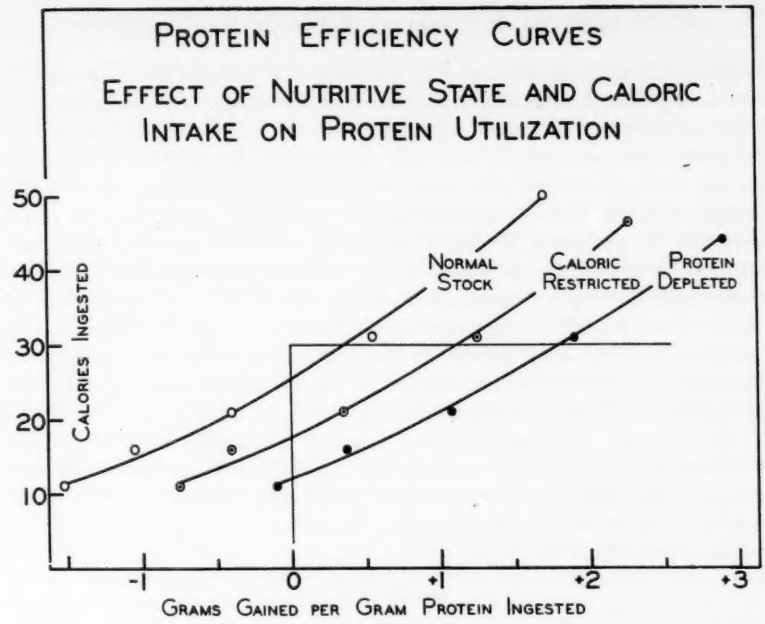

CHART 7. Protein efficiency curves. Horizontal line is drawn at 30 cal., approximate energy requirement of animals used in study.

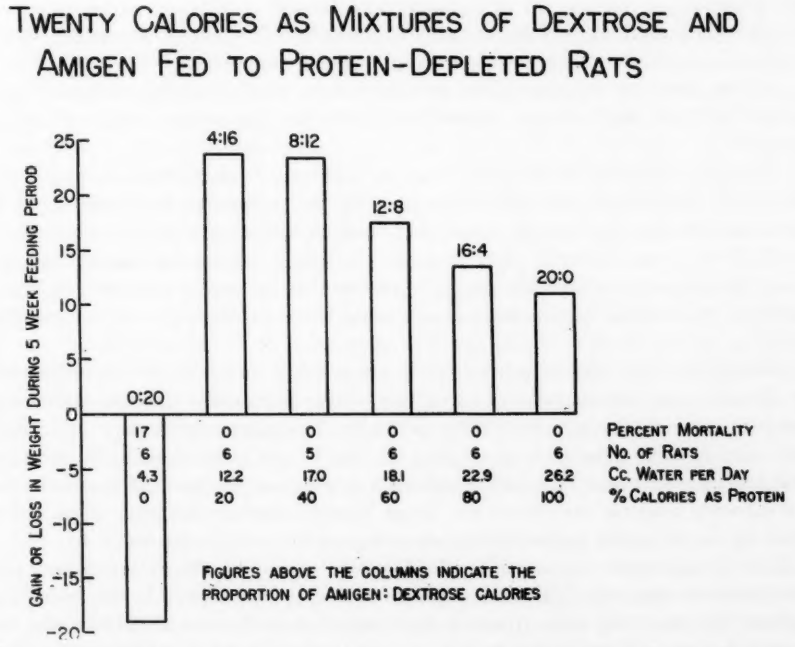

CHART 8. Change in weight of protein-depleted animals given either 20 cal. as dextrose or 20 cal. in various proportions of dextrose and protein hydrolysate (amigen®) for 5 wk

depleted animals receiving 20 calories as dextrose, or 20 calories as various mixtures of dextrose and protein hydrolysate, or 20 calories as hydrolysate. The composition of the diets was as described before and the experiment was continued for five weeks. The largest weight gain was achieved with 20% of the total calories in the form of protein hydrolysate although the gain with 40% of the calories as hydrolysate was only slightly less. Higher proportions of protein hydrolysate resulted in progressively lower weight gain, so that the proportion of calories as protein and carbohydrate is significant for growth. Protein hydrolysate alone resulted in a small gain in weight, and dextrose alone resulted in a loss in weight. If both substances were used solely for energy purposes (since 20 calories is less than the energy requirement) the same changes in weight would have been expected with the single substances, and with each mixture, since carbohydrate and protein supply 4 calories of potential energy/gm. But the animals receiving dextrose alone lost 19 gm. in weight and the animals receiving hydrolysate alone or mixed with dextrose gained 11 to 23 gm., indicating utilization of some of the hydrolysate for tissue synthesis.

The water requirement increases as the protein intake increases so that there is a 500% increase in water intake due to feeding the hydrolysate. The mortality figure for the animals on the dextrose diet appears to be a chance observation as evidenced on repetition of the experiment.

Discussion

Recently it has been alleged that calories have priority over other nutritional requirements of the body, so that if the total energy requirements of the body are not met, all the protein in the diet will be catabolized for energy. Specific quotations will illustrate this point:

"Parenteral nutrition will succeed only if the caloric demands of the patient who is unable to eat can be met, either parenterally, or from his own stores."[3]

"In the absence of adequate caloric nourishment the amino acids appear to be stripped of their nitrogen which is then excreted, and the remaining carbohydrate is utilized for energy."[2]

"Of all the dietary essentials calories must be accorded a fundamental role, representing as they do the thermal units which supply energy for intermediary metabolism, and the caloric intake must obviously be in excess of basal requirements, if it is to supply energy essential for tissue synthesis. Otherwise, the body will sacrifice fat, carbohydrate and tissue protein in order to obtain energy; in consequence, an inadequate supply of dietary calories will continue thereby to act as a limiting factor in the process of tissue synthesis."[4]

This emphasis on calories has been widely interpreted to mean that protein hydrolysates as currently used with dextrose and supplying 400 to 700 calories/l. result in no tissue synthesis, since the hydrolysate will be used only for energy requirements. It is, therefore, considered by some workers as almost essential to use an emulsion of fat to supply total energy requirements.[14] Since fat emulsions suitable for parenteral administration are not currently available for clinical use, it has become customary for many physicians to decry the use of protein hydrolysates in admixture with 5 or 10% dextrose.

There is agreement that ingested protein will be used most efficiently for tissue protein synthesis when the full caloric needs of the body are supplied by fat and carbohydrate. This point has been repeatedly demonstrated since the time of Rubner, who first showed that the addition of carbohydrate to the diet of a fasted dog reduced nitrogen loss

in the urine. However, it has been shown that part of ingested nitrogen can be used for tissue protein synthesis even though the full energy requirements are not met.

For example, Bosshardt et al.[6] have shown that mice gain in weight and utilize some 10% of ingested protein for body growth even when the caloric intake is only one-half of adequate. Similarly, Allison and his associates[5] showed that adult dogs, restricted to 50% of their caloric requirements, retained nitrogen to the same extent as animals receiving a full caloric complement. Swanson[7] demonstrated that protein-deficient rats did not excrete significantly larger quantities of urinary nitrogen when the caloric intake was reduced to 75% or to 50% of *ad libitum* intake, but only increased when the caloric intake was reduced to 25% of that ingested voluntarily. Finally, while Benditt et al.[8] emphasized that the utilization of protein by protein-depleted rats was not increased by the addition of more calories than 1240/m² surface area (maximal for most efficient utilization), his data also show that retention of nitrogen by these animals occurred at a caloric intake of 540/m².

The experiments of the present investigators have been designed to determine whether carbohydrate (dextrose) with or without protein (protein hydrolysate) is to be preferred for nourishment, when full caloric requirement cannot be supplied. The results clearly demonstrate that under various conditions of nutritional stress—protein depletion, partial starvation, scalding and full feeding—animals receiving insufficient calories as dextrose formed less tissue protein than those receiving a portion of their isocaloric intake as a protein hydrolysate. Carcass analyses showed that the better weight performance was not due to tissue water, but was demonstrable as larger stores of body protein.

It is obviously essential to describe what is meant by an adequate or optimal energy intake. This is not simple to define for the rat. The variation in the basal energy requirement is large (16); and factors of age, nutritional status, sex, environmental temperature and activity affect the total caloric need. Rats weighing 100 gm. maintained their weight by feeding 22 calories daily, which agrees with a value calculated from Rubner's formula for surface area using an average value of 1050 calories/m²; i.e., 20.6 calories. However, this caloric intake is insufficient to permit growth. The authors have accordingly estimated the energy requirement of 100 gm. growing rats as 30 calories/day. They have used as the optimal energy requirement of the rats subjected to nutritional stress the amount ingested when offered the diet *ad libitum*.

The present experiments show that when the caloric intake is only 25% of the *ad libitum* intake the protein-depleted animals maintained weight on the diet containing protein, whereas animals receiving dextrose only lost weight. The other three groups of animals showed no significant differences in weight or composition with or without protein hydrolysate when the caloric intake was as low as 25% of *ad libitum* intake. At higher caloric levels the animals were able to utilize some ingested protein for tissue synthesis. The amount that is used for tissue synthesis is related to factors other than caloric intake. The caloric need has priority over other body demands only when the caloric intake is 25% or less of *ad libitum* intake.

The thesis that protein cannot be used to spare body protein when the energy intake is suboptimal finds support in the studies by Gamble[15] who studied the loss in body protein of normal men living on a raft in the ocean. His study was designed to determine the relative importance of food and water for castaways, when both available food and water were limited. He observed that glucose 100 gm. reduced the loss in body protein

to half that lost during complete starvation, and that the addition of protein 43 gm. did not further decrease the protein loss. It is to be noted that normal individuals subsisting on full caloric and adequate nitrogen intakes were studied, and not subjects previously subjected to nutritional stress. Gamble has recently stated[16] that persons with extensive depletion of body protein may not respond to caloric deficit as do life-raft subjects in normal nutritive states.

His findings are in essential agreement with those reported here. Well-fed organisms suddenly subjected to a caloric restriction that might be estimated as 1/4 or 1/5 of their optimal intake do not use ingested protein for the synthesis of new tissue. The magnitude of need for protein is one of the most significant factors determining utilization. It has been repeatedly shown that protein-deficient man[17] retains ingested protein with avidity. Because of this fact the finding of Gamble[15] cannot be extended to the protein-depleted or malnourished individual.

An experiment to determine what proportion of calories as protein is most effectively utilized by protein-depleted animals when the total caloric intake is insufficient was performed using a caloric level of 20 calories daily. Best growth was obtained when 20 to 40% of the calories were supplied as protein. When the animals were restricted to carbohydrate (dextrose alone) they lost 19 gm. in weight while those restricted to protein hydrolysate, at the same subadequate caloric level, gained 11 gm. This would indicate therefore that while some of the 20 calories supplied as protein hydrolysate is used for energy purposes, some of the available protein is also used for tissue synthesis.

It seems logical to assume that the findings of this study are valid for parenteral feedings since it has been shown that the metabolic fate of hydrolysates orally and parenterally is essentially the same.[18]

It should be emphasized that a caloric intake adequate to meet basal metabolic and activity requirements is the *sine qua non* of proper nourishment. Protein can be most efficiently used for tissue synthesis when fat and carbohydrate supply the energy requirements. But protein can be used for body growth even in the absence of the full caloric complement when somewhat more than 25% of the energy requirements are met.

Conclusions

To determine whether a portion of ingested protein can be used for tissue growth when insufficient calories were fed, isocaloric and suboptimal amounts of calories in the form of dextrose or as dextrose and protein hydrolysate (amigen®) were fed to protein-depleted, partially starved, scalded and normal stock rats together with adequate vitamins and minerals. It is concluded that:

1. The greater the need for protein, the greater is the utilization of ingested nitrogen for new protein synthesis under conditions of caloric limitation. Protein-depleted rats are able to build new protein tissue even when basal energy requirements are not completely supplied.

2. Protein depleted, partially starved, scalded and stock animals retain or gain more weight when fed adequate or suboptimal quantities of the hydrolysate-dextrose diet than when fed isocaloric quantities of the dextrose diet.

3. Stock animals with no pre-existing protein loss, and in good nutritive condition, do not utilize dietary nitrogen for tissue building when the caloric intake is suboptimal.

4. When the caloric intake is less than that required to meet the estimated basal

energy needs, a diet supplying approximately 20% of the calories as protein supported better growth than those supplying more or less than this amount.

ACKNOWLEDGMENT

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SPANISH ABSTRACT

Utilización del Nitrógeno en Insuficiencia Calórica

Para determinar si una parte de la proteína ingerida puede ser usada para crecimiento de tejido cuando se administran calorías insuficientes, se alimentaron grupos de ratas isocalóricamente, y con cantidades subóptimas de calorías bajo la forma de dextrosa o de dextrosa e hidrolisado proteico (Amigen), que habían sido previamente nutridas con dieta ad libitum sin proteínas o con dieta com-

pleta pero insuficiente, o con dieta adecuada en cantidad y calidad que se traumatizaron por inmersión en agua caliente, y finalmente ratas alimentadas adecuadamente.

Los autores concluyeron:

1° Entre mayor es la necesidad de proteínas, más grande es la utilización del nitrógeno ingerido para nueva síntesis protéica bajo condiciones de restricción calórica. Las ratas con depleción proteica fueron capaces de formar tejido proteico nuevo aún cuando los requerimientos energéticos basales no sean completamente satisfechos.

2° Las ratas con depleción proteica subalimentadas, traumatizadas por inmersión en agua caliente, o normales, retienen o ganan más peso cuando se alimentan adecuadamente o con cantidades subóptimas de la dieta de hidrolisado y dextrosa que cuando se alimentan con cantidades isocalóricas de dieta-dextrosa exclusiva.

3° Los animales "stok" sin pérdida previa de proteínas y en buenas condiciones nutricionales no utilizan nitrógeno para formar tejido cuando la ingesta calórica es subóptima.

4° Cuando la ingestión calórica es menos que la requerida para llenar las necesidades de energía basal, una dieta que suministra aproximadamente el 20% de las calorías bajo le forma de proteínas sostiene mejor crecimiento que aquélla que suministre una cantidad de proteínas mayor o menor.

Mead Johnson Research Laboratories

MASSIVE HYDROPS OF THE GALLBLADDER PRODUCING PYLORIC OBSTRUCTION IN A SEVEN YEAR OLD BOY

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Cincinnati

THE first attempt to assemble all published cases of gallbladder disease in children was made by Potter[1] in 1928. He collected 226 cases in the literature from 1722 to 1927 and added four of his own. Ten years later he[2] brought the total number to 432 cases, including six more of his own. Recently Ulin, Nosal and Martin[3] extended the survey through 1948 and, including those of Potter, they found 475 cases, to which they added one new one.[4] But after subjecting the reported cases to critical analysis, the latter authors rejected 149 as unacceptable, leaving 326 cases which meet their diagnostic criteria for gallbladder disease in children 15 years of age and under. If the congenital anomalies of the biliary tract are excluded, acute cholecystic disease in childhood must be regarded as very unusual.

Most observers are agreed that inflammatory disease of the gallbladder in childhood usually occurs as a complication of acute systemic infections. The relationship between cholelithiasis and hemolytic anemia is well known, but stones do form in the gallbladders of children under other circumstances. Typhoid fever was once a common precursor of both stones and inflammation in children as well as in adults, but effective prophylaxis during the past 30 years has made this a negligible factor. In acute cholecystic disease of childhood jaundice is more common than it is in adult cases but stones are less common, and Ulin and his associates comment that "obstructive jaundice due to common-duct stone is quite unusual. Jaundice, when present, is usually inflammatory in origin." They further note that "in reviewing the reports one is impressed by the fact that most childhood cases resemble very closely in their signs and symptoms those seen in adult life." It is interesting, however, that gallbladder disease of children more commonly affects males than females (3:2) while in adults females are much more commonly affected, in the proportion of 4:1.

The case here considered is reported not only because of the relative rarity of gallbladder disease of any kind in children, but more particularly, because of its unusual clinical manifestations.

CASE REPORT

History: A 7 yr. old white male had been perfectly well until 4 days prior to admission. He contracted a severe, febrile respiratory infection with delirium and temperature ranging to 40.5°C. He was seen at home and treated with chloramphenicol (chloromycetin®). Temperature returned to normal in 48 hr., but he remained weak and was required to stay in bed. Thirty hours prior to admission he developed a severe and sudden pain in R upper abdominal quadrant and vomited once. Vomitus contained no blood. Pain persisted. Eighteen hours before admission he was given a saline enema with good return of normal stool which showed no blood. He had no other bowel movements during 30 hr. prior to admission. A tender mass was palpable and visible in R upper quadrant. Child was admitted to hospital with a tentative diagnosis of intussusception.

Past History: At age of 2 yr., boy had an umbilical hernia repaired with excision of umbilicus. A month before admission he had been treated for ascariasis.

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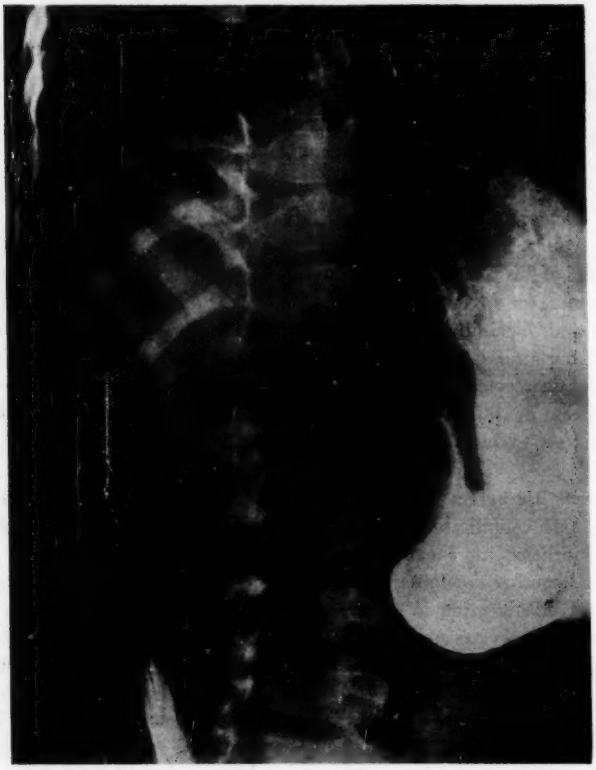

FIG. 1. Oblique film of abdomen following several swallows of barium. Rounded extrinsic mass is demonstrated, which impinges on antrum of stomach. No barium passed pylorus during observation period of 1¼ hr. Barium was then removed by suction.

Clinical Findings: The findings on admission were as follows:

Temperature 37.0°C.; PR 122/min.; resp. 20/min. Patient did not appear to be in severe distress. There was a slight residual acute pharyngitis. Skin and sclerae were clear.

There was marked tenderness and muscle spasm in epigastrium and R upper quadrant and, in spite of muscle splinting, a tender mass could be felt in R upper quadrant. At this time, however, it was not visible. Rebound tenderness was present, both locally, and referred from other parts of abdomen. Mass was estimated to be about 6.0 cm. in diameter. Except for well-healed scar of excised umbilicus, abdomen was normal. Peristaltic sounds were normal.

Hgb. 10.7 gm./100 cc., WBC count 4.5 thousand/cmm. Urine: negative.

Initial radiographic studies consisted of 3-positional films of abdomen. In all 3 positions a curious mass, of soft tissue density, was seen to occupy the usual position of R half of stomach. Gas bubble was not seen in the gastric fundus. A small amount of gas was normally distributed in the small bowel. Colon contained enough gas to visualize it quite well and ascending and transverse portions were demonstrated with sufficient clearness to exclude diagnosis of ileocolic intussusception. Colon was not distended.

Under fluoroscopic control patient was given several swallows of thin barium suspension. Stomach was found to be moderately distended with fluid, and no gas shadows could be seen. Barium fluid would not pass through pylorus, which appeared to be obstructed by a smooth, rounded, extrinsic mass impinging upon the antrum along greater curvature (Fig. 1). Hepatic flexure of colon appeared to be displaced downward by the mass. Patient was observed at intervals under fluoroscope

for a period of 1¼ hr. and no barium was seen to pass into duodenum. It became apparent that pyloric obstruction was present, due to a large extrinsic mass of undetermined origin. Nature of this mass was not suspected until it was exposed at surgery.

Operation: Mass proved to be a huge hydrops of gallbladder. Aspiration of contents with a needle yielded "white bile" only faintly tinged with yellow. Because of tense distention of the viscus the presence or absence of stones could not immediately be determined. Cystic duct was extremely narrow and at the angle between it and the common duct a large lymph node, about 1.0 cm. in diameter, was encountered. In the angle between the common duct and the second portion of the duodenum, a larger lymph node, measuring 2.25 × 1.25 cm., was found. Common duct was not dilated, and no stones could be felt in it, in cystic duct, or in antrum of the gallbladder. Spleen was about twice normal size, weighing an estimated 200 to 225 gm. This was thought to represent an acute splenic tumor associated with the recent severe febrile illness. Remainder of the abdomen was negative. Gallbladder was only moderately thickened, with only slight loss of peritoneal sheen and no serosal exudate. Liver appeared to be normal.

Gallbladder was removed and lymph node in the cystic duct angle was removed along with it (Fig. 2). Larger node lying against distal third of common duct was removed separately. In so doing, moderate bleeding was encountered, the ultimate control of which required a small pack of oxidized cellulose gauze. Fossa of Morison was drained with a single cigarette drain through a stab wound in the flank, and the working incision was closed.

Gross specimen, fixed in 10% formalin, consists of a markedly distended and elongated gallbladder measuring 11 cm. in length and 5 cm. in greatest diameter. Lining is light tan and slightly reticulated and is without evidence of ulceration. Bile contained within bladder is clear and slightly mucoid. An ovoid lymph node 1 cm. in diameter is present at neck of gallbladder and another 1.5 cm. lymph node is received separately. Lymph nodes consist of a moderately firm, grayish-white lymphoid tissue.

Microscopic sections show an intact mucosal surface consisting of columnar epithelial cells. Occasional small folds project into lumen, but in general surface is flattened with loss of normal folds. Lamina propria is moderately congested. Muscular layer is thinned and stretched and fibers are spread apart by edema fluid. A slight lymphocytic and neutrophilic infiltration is present throughout the lamina propria and muscular layer.

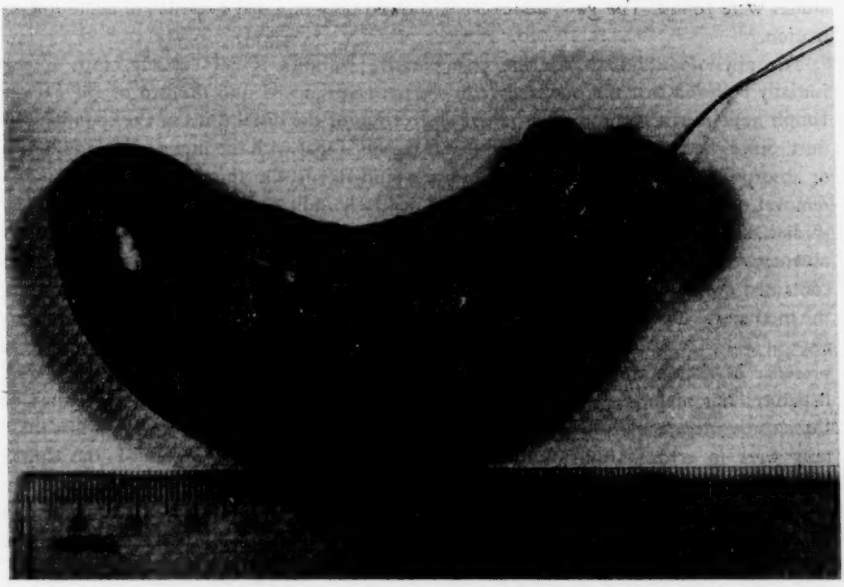

FIG. 2. Photograph of gallbladder taken shortly after operation. Lymph node described in text has retracted somewhat. It originally lay snugly against narrow cystic duct.

TABLE 1

LABORATORY STUDIES

Date	Bil. tot.	Bil. dir.	Bil. ind.	Ceph. floc.
12-16-51	5.0	4.0	1.0	4+
12-20-51	7.4	5.8	1.6	3+
12-24-51	2.7	2.0	0.7	4+
12-27-51	2.3	1.8	0.5	—
12-19-51 12-22-51 12-26-51	Urine urobilinogen—Negative			

Lymph nodes are hyperplastic and chronically inflamed.

Diagnosis: Hydrops of the gallbladder; acute cholecystitis, mild chronic hyperplastic lymphadenitis.

Postoperative Course: On 1st postoperative day urine became dark and on 2nd day skin and sclerae were icteric. Maximum temperature was 37.5° C. Throughout postoperative course stools remained normal in color and contained bile pigment. Jaundice reached maximum on 6th postoperative day. Laboratory studies are tabulated in table 1.

Jaundice cleared rapidly thereafter. He was discharged from hospital on 13th postoperative day. His course since he left hospital has been entirely satisfactory.

DISCUSSION

This case presented a number of interesting questions, for some of which no unchallengeable answer can be offered. The hydrops of the gallbladder would appear to have been the result of inflammatory obstruction of a narrow cystic duct, possibly augmented by the impinging lymph node. As indicated in the report of the surgical pathologist, no stones were found. The gallbladder itself showed only minimal evidence of acute inflammation.

The physiological basis for the postoperative jaundice is not entirely clear. It was initially believed that the oxidized cellulose pack introduced into the bed of the excised lymph node might be producing partial obstruction of the distal third of the common bile duct. Since the area had been drained it was reasoned that with the liquefaction and escape or absorption of the cellulose, the jaundice would recede. On this basis re-operation and removal of the pack did not seem to be immediately indicated. When the first laboratory studies were returned, the strongly positive cephalin flocculation test argued against obstructive jaundice. The stools, whether spontaneous or induced by enema, uniformly contained normal amounts of bile pigments and if the jaundice were obstructive in origin, the mechanical block must necessarily have been incomplete. Because of the prompt appearance of a 4+ cephalin flocculation test, a slight increase in the prothrombin time and the presence of normal amounts of bile in the stools, the jaundice was interpreted as being hepatocellular in origin. The disturbing feature of this interpretation was the return of three consecutive negative tests for urinary urobilinogen. It can only be assumed that these tests were in error. Although the blood sedimentation rate was increased, the child's temperature remained normal and he looked and felt well.

It was at length concluded that the manipulation at surgery and the excision of the two lymph nodes had resulted in an acute intrahepatic cholangitis, and on this assumption the choleretic action of magnesium sulfate was tested, with a prompt and favorable effect. This, in conjunction with the laboratory evidence, suggested that the oxidized cellulose pack did not play any part in the postoperative jaundice.

There was some discussion as to whether cholecystectomy should have been done, since the symptoms could have been relieved by cholecystostomy, without sacrificing the gallbladder. This is a difficult question to answer since few surgeons have enough personal experience with gallbladder disease in children to justify a dogmatic opinion. In three of Potter's cases cholecystostomy alone was done. Their ages were 11, 6 and 4½ and they were reported to have remained well for 3½ years, 3 years and 6 months, respectively. Their subsequent course is not known. Edington[5] performed cholecystostomy on a girl 15 years of age who remained asymptomatic for seven years. She then began having recurrent pain and at the age of 24, nine years after the cholecystostomy, she developed a spontaneous external biliary fistula and cholecystectomy became mandatory.[6] This patient had cholelithiasis at both operations, while in the case reported here there were no stones.

Nevertheless, on the basis of adult experience, it is known that cholecystostomy is not often satisfactory as a definitive procedure and is attended by a high incidence of recurrent symptoms ultimately requiring cholecystectomy. In most clinics the operation is reserved for elderly or critically ill patients whose condition does not permit a more definitive procedure. In such circumstances cholecystostomy may be life-saving. It can be argued that there were no stones present in the case here reviewed and that the gallbladder showed only a minimal degree of acute inflammation. It should be remembered, however, that neither of these facts could be proved at the operating table, since opening the gallbladder might have contaminated an otherwise clean field. Moreover, the postoperative hospital stay is appreciably longer when cholecystostomy is done. In general the reports of cholecystectomy in children indicate excellent long-term results with good adjustment to loss of the gallbladder and either minimal digestive disturbance or none at all. It is believed, therefore, that cholecystectomy was the procedure of choice in this case.

Summary

A case of massive hydrops of the gallbladder producing pyloric obstruction in a seven year old boy is presented. Jaundice was not present initially but occurred as a transitory postoperative complication attributed to cholangitis and hepatitis. The merits of cholecystectomy as compared with cholecystostomy in such cases have been briefly discussed.

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Spanish Abstract

Hidropesía Masiva de la Vesícula Biliar que Produjo Obstrucción Pilórica en un Niño de Siete Años

Los autores presentan un caso de hidropesía masiva de la vesícula biliar que produjo obstrucción pilórica en un niño de siete años de edad. No se presentó ictericia inicialmente, pero la desarrolló en forma transitoria como una complicación post-operatoria atribuída a colangitis y hepatitis. Los méritos de la colecistectomía, que favorecen los autores en estos casos, comparados con la colescistostomía, son discutidos brevemente.

3231 Burnet Avenue

HEMATOLOGIC ADJUSTMENTS TO CYANOTIC CONGENITAL HEART DISEASE

By ABRAHAM M. RUDOLPH, M.D., ALEXANDER S. NADAS, M.D., AND WAYNE H. BORGES, M.D.
Boston

CYANOTIC congenital heart conditions for which surgery is not yet available present a perplexing problem of conservative management. Decreased oxygen content of the blood with resulting tissue anoxia is one of the main causes of disability in cyanotic congenital heart disease. Augmentation of pulmonary blood flow by means of surgery in selected cases primarily increases oxygen content of the blood without immediately affecting oxygen-carrying capacity. The other available method of raising the oxygen content is by increasing the oxygen-carrying capacity of the blood. The organism attempts to attain this physiologically in cyanotic congenital heart disease by the development of polycythemia and raised hemoglobin content. This process is comparable to the stimulation of red cell and hemoglobin formation at high altitudes, where low oxygen tensions may produce anoxia.

Several infants and children with cyanotic congenital heart disease have recently been encountered in this clinic, showing polycythemia, but with hemoglobin levels in or below the average range for their age. This suggested that the anoxia, although severe enough to stimulate polycythemia, for some reason failed to give rise to a corresponding increase in hemoglobin and oxygen capacity. Although the hemoglobin level itself was normal, it was low when compared to the polycythemic erythrocyte counts. Anemia, with low mean corpuscular volume, because of the microcytic character of the red cells, and low mean corpuscular hemoglobin, because of deficiency of hemoglobin per red cell, was actually present. The authors have termed this phenomenon "relative anemia" of cyanotic patients.

The purpose of this study was (1) to find a means of increasing the hemoglobin and thus the oxygen-carrying capacity of these patients with relative anemia, (2) to determine whether any clinical improvement paralleled this increase and (3) to attempt to explain the origin of this relative anemia by following the natural course of the hematologic changes in congenital heart disease from the early neonatal period.

MATERIAL AND METHODS

Seven patients with cyanotic congenital heart disease and relative anemia were studied for their response to iron administration. The iron preparation used in all cases was ferrous sulfate in doses of 150 mg. daily, supplying 30 mg. of available iron.* This was administered between meals in watery or syrupy vehicles not containing phosphate, since it is known that phosphate disturbs iron

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* The iron preparation used was Fer-in-Sol, supplied by Mead Johnson & Company, in doses of 1.2 cc. daily.

absorption by the intestine. No note of optimism concerning possible improvement with iron therapy was conveyed to either the child or the parents. Careful clinical assessment was made at each visit and venous blood collected for erythrocyte count, hemoglobin content and hematocrit. Blood viscosity studies were performed on most samples collected.

A second group of 8 newborn infants with congenital heart disease was examined at intervals of 2 to 4 wk., from birth, for periods of 3 to 9 mo. in order to follow the natural course of their hematologic development. The diets of these infants were not supplemented with iron and differed in no way from those generally used in feeding normal infants. Studies similar to those in the first group were carried out.

Venous blood was collected using oxalate[1] as the anticoagulant. Red blood counts were performed with U. S. Bureau of Standard pipettes, Hgb. determined with the Evelyn colorimeter, and hematocrits done by the Wintrobe method. The viscosity measurements were done in 33-second Ostwald tubes at 37° C. This method of viscosity determination was used because of its simplicity.

TABLE 1

RESPONSE OF "RELATIVE ANEMIA" OF CYANOTIC CHILDREN TO IRON THERAPY

		Age	Diagnosis	Before Iron		Period of Iron	After Iron	
				RBC	Hgb.	Therapy	RBC	Hgb.
1.	L.B.	1 10/12	T. of F.*	5.8	10.6	6 mo.	10.5	22.6
2.	J.B.	4 2/12	T .of F.*	6.81	10.35	4 mc.	6.33	16.45
3.	C.B.	2	T. of F.*	6.75	14.0	5 mo.	9.08	20.9
4.	D.D.	2 1/12	Transposition with P.S.†	5.25	12.6	8 mo.	8.5	26.5
5.	S.E.	2 3/12	T. of F.*	9.3	13.2	2½ mo.	10.7	26.8
6.	P.K.	5/12	Transposition	7.0	12.0	2 mo.	7.5	16.0
7.	K.W.	1 3/12	T .of F.*	6.09	10.1	5 mo.	10.68	22.9

* Tetralogy of Fallot.

† Pulmonic stenosis.

RESULTS

A. Study of Infants and Children with Relative Anemia:

Table 1 indicates the age, diagnosis and erythrocyte and hemoglobin levels before and after iron therapy and the periods of therapy to achieve these results in the seven infants and children with relative anemia. It may be seen that all patients showed a remarkable rise in total circulating hemoglobin following oral iron administration. Within 10 to 14 days, a significant reticulocytosis developed, comparable to that noted in response of iron-deficiency anemia responding to iron medication. Reference to charts 1 to 4 indicates the nature of the change that develops. The direction of changes in hematocrit and hemoglobin values is that associated with the production of cells of more normal size and of more normal hemoglobin content. (Case 3 did not show an increase in cell size and Cases 1 and 6 did not show significant increases in hemoglobin content per red cell.) However, whereas hematocrit and hemoglobin values of the normal child without cyanosis, recovering from iron-deficiency anemia, will rise to only 14-15 gm., in these cyanotic children the increases went beyond the usual normal range probably because of the constant anoxic stimulus.

The clinical condition of the patient could be well correlated with the hematologic status. These patients all had numerous symptoms commonly associated with anoxia, viz., irritability, anorexia, poor weight gain, "spells" (attacks of severe cyanosis with loss of consciousness), dyspnea and cyanosis. Not all patients presented every symptom men-

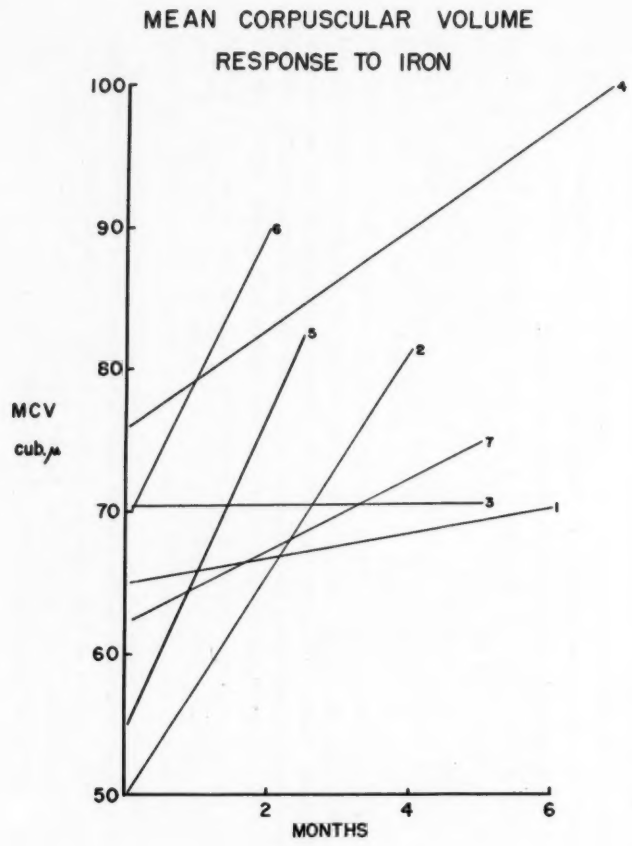

CHART 1

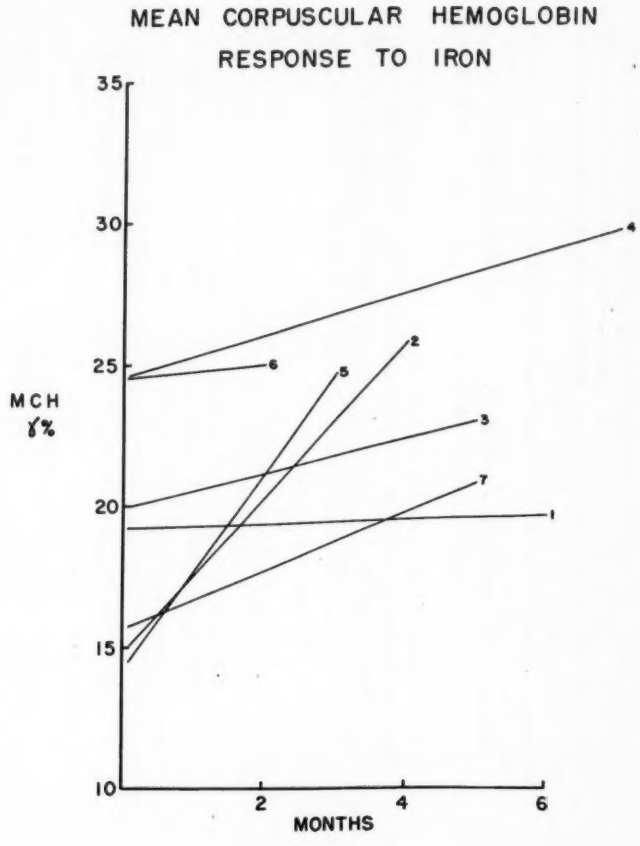

CHART 2

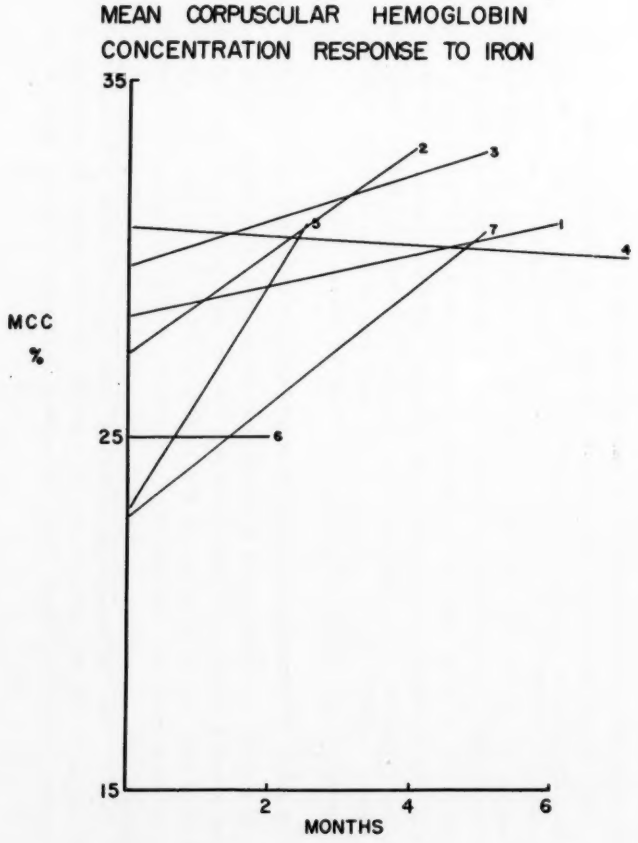

CHART 3

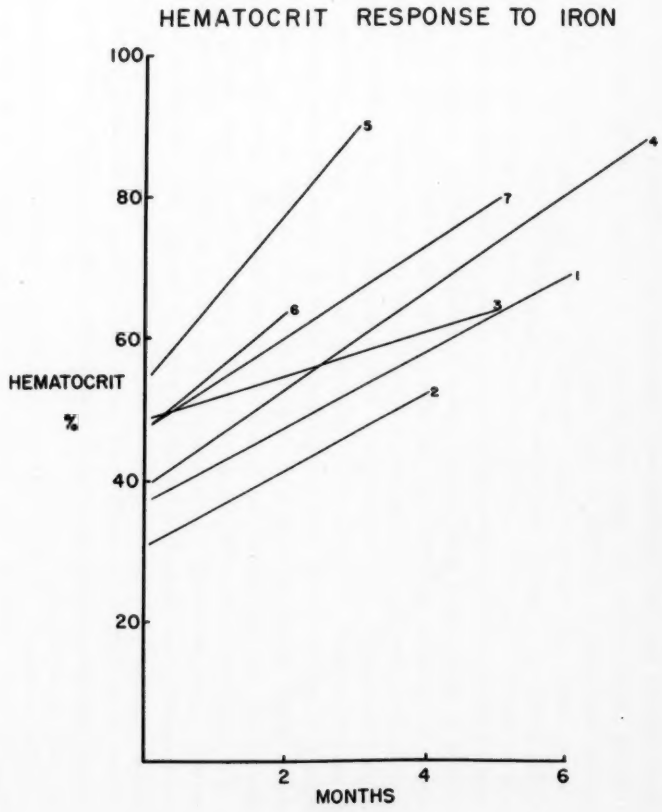

CHART 4

tioned, but the first three symptoms were consistently present. Patients 1, 3, 5 and 7 had frequent "spells" (3 to 4 a week) and Patients 1, 2, 3, 4 and 5 all had dyspnea and exercise intolerance in addition to these symptoms.

As in simple iron-deficiency anemia responding to therapy, these children exhibited all the gratifying changes of rapid improvement of appetite, decrease in irritability, and gain in weight, often before any significant changes in red cell count or hemoglobin occurred. Decrease in the number of spells, improvement of exercise tolerance, and rapid increase in weight, with general improvement in behavior, gradually occurred over the next 2 to 6 months. Associated with this improvement was a marked accentuation of the cyanosis. Since the degree of cyanosis is dependent on the total amount of circulating reduced hemoglobin, a rise in hemoglobin level, unaccompanied by a significant change of oxygen saturation, will result in an increase in the depth of cyanosis. However, an increase in oxygen capacity, with no significant change in oxygen saturation, provides a greater actual quantity of oxygen available to the tissues, in spite of the increase in cyanosis; and this may explain the clinical improvement shown during this phase.

The initial enthusiasm about the good clinical response to iron in these children was, however, rather short-lived in some instances. The clinical improvement, associated with severe cyanosis, was maintained for several weeks or months, after which there was a gradual regression with return of anoxic symptoms. Irritability, return of dyspnea, and increase in the number of "spells" were noted. On reviewing the hematologic data, it appeared that the clinical status could be fairly closely correlated with the blood changes, especially the hematocrit.

As the hematocrit rose from the initial relatively low figure, the patient's symptoms improved, until a level of 70% was reached. Progressive increase of the hematocrit above this figure resulted in a progressive deterioration of the clinical condition. Chart 5 illustrates these features mentioned, as encountered in Case 5.

This clinical deterioration with excessive increase in the hematocrit suggested that the reappearance of symptoms was in some way related to red cell mass. In an attempt to explain this phenomenon, viscosity studies were performed on all subsequent blood samples collected in this study. Chart 6 represents the relationship of specific viscosity to hematocrit in graphic form, as determined from the blood samples collected. The relationship is in the form of a hyperbolic curve; at lower hematocrit levels, a fairly large rise of hematocrit is required to produce any significant change in viscosity. At higher hematocrit levels, however, minor increases of hematocrit produce marked increases in viscosity. The critical region in this curve seems to lie in about the 75 to 80% hematocrit range, corresponding rather well with the clinical findings.

B. Study of Hematologic Course of Newborn Infants with Congenital Heart Disease:

In order to try to understand the mechanism and the time of appearance of the relative anemia encountered in older infants and children, eight infants in whom congenital heart disease was discovered in the first 10 days of life were followed. These patients could be divided into three groups: 3 noncyanotic, 3 mildly cyanotic and 2 markedly cyanotic.

Chart 7 shows the hemoglobin and red cell count progress in three noncyanotic cases as compared with the normal curve.[2] It is obvious that these infants demonstrated the expected anemia of infancy. Their hematologic development did not differ in any

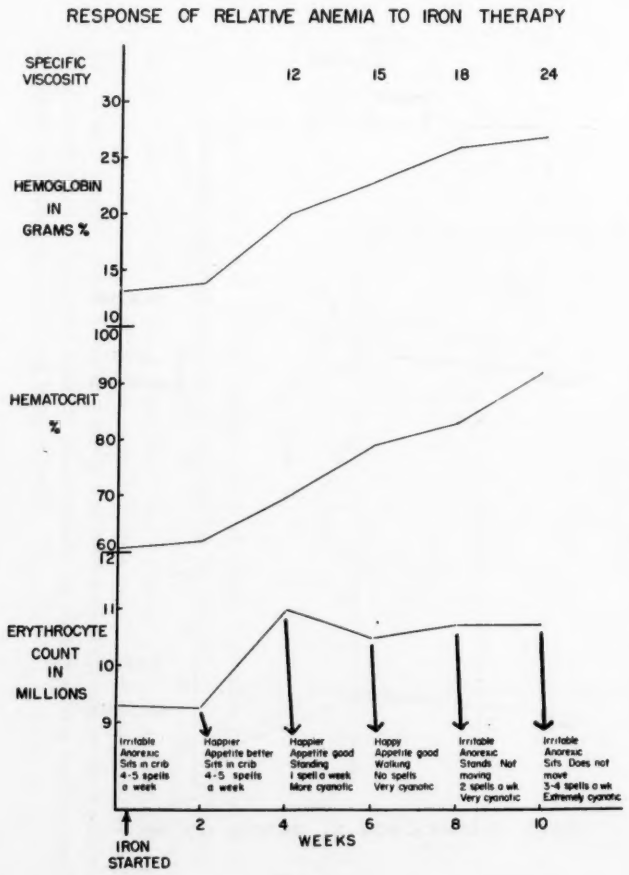

CHART 5

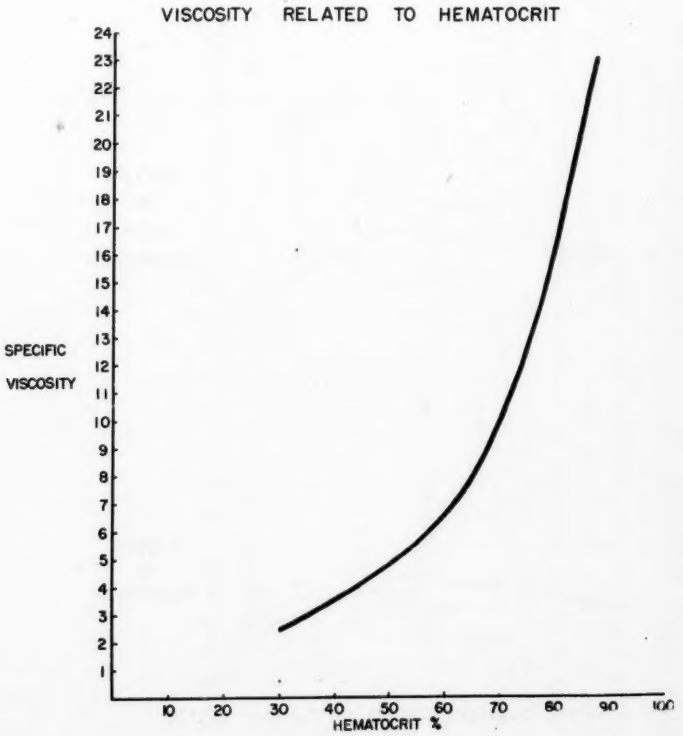

CHART 6

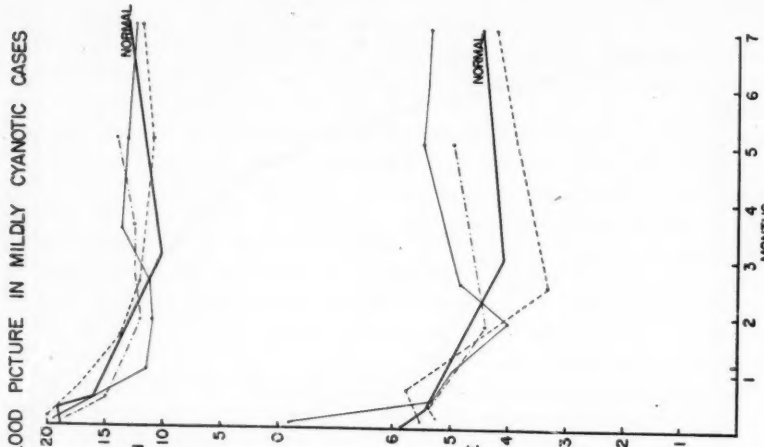

CHART 8

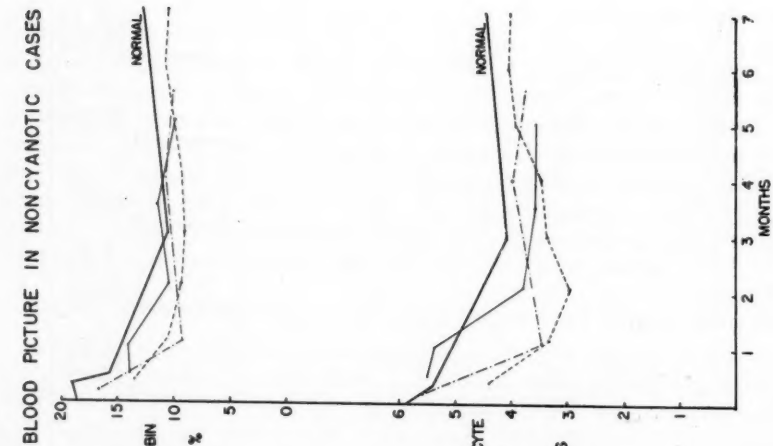

CHART 7

significant way from the normal, either in regard to the extent of the changes or the time of their occurrence.

The blood picture of the three mildly cyanotic babies is presented in chart 8. The two infants with minimal cyanosis behaved as did the noncyanotic cases. In the third infant, with somewhat more cyanosis, the normal trend to physiologic anemia developed at about the third month. Thereafter, the red cell count rapidly attained mild polycythemic levels, whereas the hemoglobin approximated the normal values for the age. This resulted in slight relative hypochromic microcytic anemia.

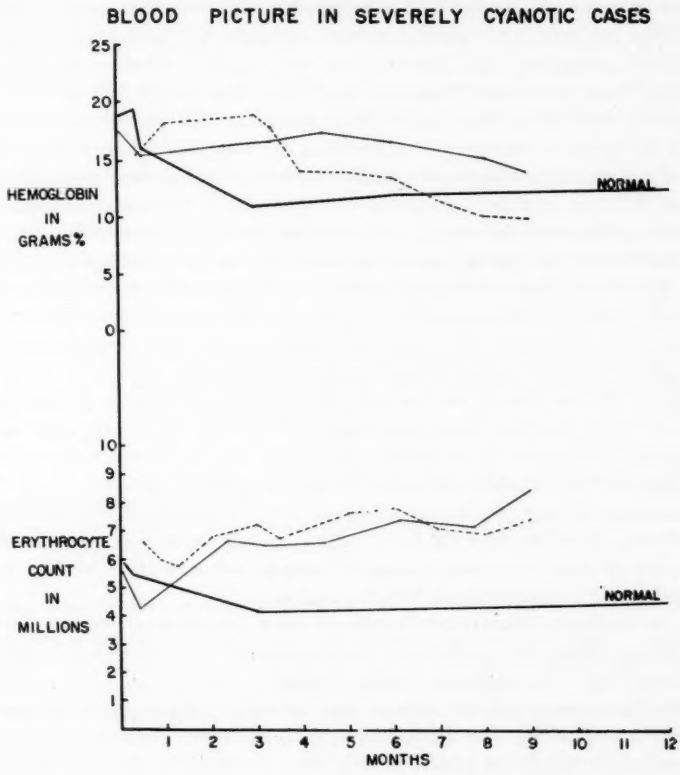

CHART 9

In the two infants with marked cyanosis (arterial oxygen saturation 22% and 34%, respectively), the physiologic anemia of infancy did not develop (chart 9). The high levels of erythrocyte count and hemoglobin of the newborn infant were maintained until about the third to fourth month. A divergence between the red cell count and hemoglobin then developed, with a gradual increase in red cell count and a fall in hemoglobin, so that the "relative anemia" noted in the first group was quite well developed by the eighth to ninth month of life. Associated with the manifestations of relative anemia was the onset of irritability, poor weight gain and, later, anorexia.

Comment

Anoxic anoxia, due to ascent to high altitudes, with low oxygen tensions, or due to respiratory disease, causes a "compensatory" polycythemia with a corresponding rise of hemoglobin. This increases the oxygen-carrying capacity, so that a greater quantity of oxygen can be carried to the tissues at a somewhat lower tension. In cyanotic congenital heart disease, there is a persistent anoxic stimulus to the bone marrow, of greater or lesser degree; the marrow responds, and polycythemia develops. In most children thus affected, the hemoglobin increase approaches the rise in erythrocyte count, but several have been encountered who manifest polycythemia but no corresponding rise in hemoglobin. This condition of "relative anemia" presents the pattern of iron-deficiency anemias, with microcytosis and hypochromia, and responds extremely well to iron administration. Anemia in cyanotic patients has been recognized previously, and Taussig[3] used repeated small blood transfusions in its treatment. The present authors have also employed this form of therapy with good effect in some babies with severe symptoms. Taussig also warns of the danger of vascular thromboses with marked polycythemia.

In these children, iron therapy results in a rapid rise of hematocrit and hemoglobin, with a less significant rise of the red cell count, so that cells of normal size and normal hemoglobin content are formed. Associated with this rise of hematocrit is an improvement in the clinical signs expressing anoxia. The hematocrit level continues, however, to rise well beyond normal, probably because of the continuing anoxic stimulus. As the hematocrit level approaches 80%, there is a recurrence of former symptoms of anoxia. In the higher hematocrit ranges, blood rapidly becomes more viscous, and it is therefore suggested that the clinical deterioration after early improvement is related to increase of blood viscosity. To what extent pulmonary and systemic circulatory mechanisms and oxygen uptake are involved is not known, but studies are in progress to assess the relationship between these factors and blood viscosity in cyanotic children.

It is desirable to keep the hematocrit below 70%. However, if iron administration is stopped only after this level has been reached, it may continue to rise, probably due to availability of iron from tissue storage. It may be advisable, therefore, to stop iron administration when a level of about 60% has been attained.

Studies on newborn infants with congenital heart disease were done to investigate what factors are involved in causing this "relative anemia" in children with cyanotic congenital heart disease. Two important features evolved:

1. In the two severely cyanotic infants thus far studied, the expected postnatal drop of erythrocytes and hemoglobin did not develop. This throws interesting light on some of the hematologic changes in early life. The drop in hemoglobin and red cell count in the first 2 to 3 months of life in normal infants is not thought to be related to iron deficiency, and iron administration does not affect it (Josephs[4]). This study supports the hypothesis that this early drop is based on changes in blood oxygen tension. In the fetus in utero, the oxygen tension in the blood is only about 11 mm.Hg as compared to about 40 mm. after initiation of pulmonary respiration.[5] When the rise of oxygen tension occurs normally, the hemoglobin and red cell levels drop; but if the low tensions persist, the stimulus maintains the high fetal levels.

2. The maintenance of the very high red cell and hemoglobin levels in markedly cyanotic infants requires a large reserve of iron either from dietary or prenatal sources. It has been shown in these studies that there is a tendency for these children to develop

relative anemia after a period of normal development in the first 4 to 5 months of life. The anemia is due to iron deficiency because they require considerably more iron than normal infants to fill the excessive numbers of red cells with hemoglobin. This greater demand for iron may further be affected by the practice of maintaining a high fluid intake (usually large amounts of milk) to avoid dehydration in these infants. Consumption of iron-containing solids may thus be considerably delayed.

Summary

Several infants and children with cyanotic congenital heart disease and polycythemia, but without a corresponding increase in hemoglobin, have been encountered.

The presence of a normal hemoglobin level in cyanotic children is not sufficient evidence of absence of anemia.

These children responded well to iron therapy; they showed a rise of hematocrit and developed normal red cells in excessive amounts. Clinical improvement paralleled the rise of hematocrit.

A rise of hematocrit above 75% resulted in return of symptoms, possibly due to marked increase of blood viscosity.

Studies on newborn infants with congenital heart disease show an absence of the usual postnatal erythrocyte decrease in very cyanotic infants but revealed a tendency to the development of "relative anemia" after the third or fourth month of life.

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Spanish Abstract

Adaptaciones Hematológicas a las Cardiopatías Congénitas Cianóticas

La disminución del contenido de oxígeno en la sangre, que determina anoxia tisular, es una de las causas principales de invalidez en las cardiopatías congénitas cianóticas que aun no tienen terapéutica quirúrgica y que presentan un problema perplejo en su manejo.

Por medio de dos procedimientos es posible mejorar el estado de anoxia tisular de estos enfermos; aumentando el contenido de oxígeno de la sangre con intervenciones quirúrgicas que produzcan un incremento del flujo sanguíneo pulmonar o bien aumentando la capacidad de transporte de oxígeno de la sangre. El organismo hace un intento de lograr esto fisiológicamente en cardiopatías congénitas cianóticas haciendo una policitemia y elevando el contenido de hemoglobina en forma comparable al estímulo en la formación de eritrocitos y hemoglobina con la altitud.

Los autores encontraron algunos lactantes y niños con cardiopatías cianóticas congénitas que presentaban policitemia pero con niveles de hemoglobina en los límites o por abajo de las variaciones promedio para su edad, sugiriendo que la anoxia, aunque lo suficientemente severa para producir policitemia, por alguna razón no determinó el incremento respectivo en hemoglobina y por lo tanto el contenido de oxígeno. Aunque era normal el nivel de hemoglobina por sí mismo, era bajo cuando se comparó con las cuentas policitémicas eritrocíticas. En realidad existía anemia con promedio volumétrico corpuscular bajo debido a la microcitosis y promedio hemoglobínico corpuscular bajo debido a la deficiencia de hemoglobina por eritrocito y a la cual denominan "anemia relativa" de los pacientes cianóticos.

Llevaron a cabo este estudio tratando de encontrar la manera de aumentar la hemoglobina y por consiguiente la capacidad de transporte de oxígeno de dichos enfermos con anemia relativa; determinar si hay alguna mejoría clínica simultánea a este aumento de la hemoglobina, y tratar de explicar el origen de la anemia relativa siguiendo el curso natural desde el periodo neonatal de los cambios hematológicos en las cardiopatías congénitas.

Se estudiaron siete enfermos con cardiopatias congénitas cianóticas y anemia relativa en su respuesta a la administración de hierro y ocho recién nacidos con enfermedad congénita del corazón fueron examinados a intervalos para observar el curso natural de sus cambios hematológicos.

Los autores llegan a las siguientes conclusiones: 1.—La presencia de un nivel normal de hemoglobina en niños cianóticos no es una prueba suficiente de las ausencia de anemia. 2.—Estos niños responden bien a la terapia con hierro, muestran un aumento del hematocrito y forman eritrocitos normales en cantidades excesivas. La mejoría clínica es paralela al aumento del hematocrito. 3.—Un aumento del hematocrito arriba del 75% produjo el retorno de los síntomas, debido posiblemente a un aumento marcado de la viscosidad de la sangre. 4.—Los estudios en recién nacidos con cardiopatías congénitas muestran ausencia del descenso postnatal usual de eritrocitos en niños muy cianóticos pero revelan tendencia al desarrollo de "anemia relativa" después del tercero o cuarto mes de la vida.

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THIRD-GENERATION SYPHILIS

Report of a Probable Case

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IMPROVED methods of prevention, diagnosis and treatment of maternal syphilis have greatly reduced the opportunities to study the transmission of congenitally acquired syphilis to the third generation.

Although there are reports in the literature concerning third-generation cases, many of them fail to stand up under careful scrutiny. It has been emphasized by Moore[1] and Stokes, Beerman and Ingraham[2] that in the earlier literature the diagnosis was made either on clinical signs alone or on the basis of a positive serologic test obtained soon after birth without clinical or roentgenologic confirmation of the disease. Some of these cases must be excluded as it is now well accepted that babies born of seropositive mothers may show positive serologic tests up to 70 days after birth without actually being infected.[1]

In Japan congenital syphilis still occurs frequently and, because of economic factors, these cases often remain untreated, thus affording a greater possibility for the occurrence of third-generation syphilis.

A probable case which fulfills the criteria of Fournier and Finger[3] is presented here.

CASE REPORT

M. W. was first seen in the Nagasaki clinic of the Atomic Bomb Casualty Commission at 13 wk. of age because his mother's postpartum serologic tests for syphilis were strongly positive. Since the baby had typical syphilitic stigmata and strongly positive serologic tests a diagnosis of congenital syphilis was made. It was noted at that time that the mother had facies of congenital syphilis with severe corneal scarring. A family study (chart 1) was then made to determine whether her infant was a case of third-generation syphilis.

First Generation

A. Baby's maternal grandfather, A. S., a 62 yr. old Japanese farmer, had gonorrhea at age of 20 yr. followed by development of swelling in R inguinal region which was subsequently removed without sequelae. Fifteen years ago he developed weakness of R leg with backache which was diagnosed as neuralgia and for which he remained in bed for 3 yr. He had complained of some weakness of R leg ever since. He had never received specific antisyphilitic or penicillin therapy for any reason. He had had no previous serologic tests.

Positive findings on physical examination were hypertension of 174/84 mm.Hg, arteriosclerosis of retinal vessels, several areas of vitiligo on trunk and a "punched-out" depigmented penile scar (Fig. 1), the surface of which was covered with thin skin. Neurologic examination was normal, and there appeared to be no appreciable weakness of R leg.

On 2 occasions the Kolmer-Wassermann test was 3+ with no titre and the cardiolipin-microflocculation and Kline tests were doubtful. Examination of spinal fluid was refused.

A diagnosis of probable latent syphilis was made on basis of serologic tests, history, and penile scar.

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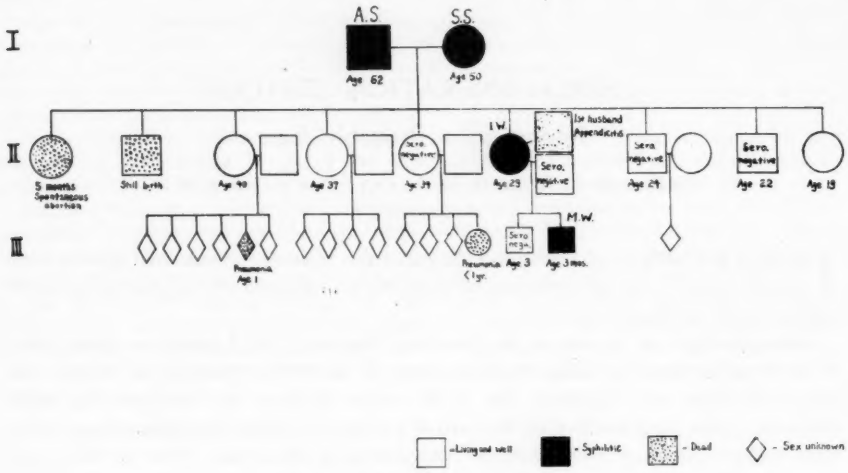

CHART 1. Family study of M. W.

B. Baby's maternal grandmother, S. S., a 60 yr. old Japanese peasant woman, gave no history of syphilitic symptoms or knowledge of infection. She had never had serologic tests, had received no specific antisyphilitic treatment (including penicillin), and had never been examined by a physician.

Her 1st pregnancy occurred at age of 18 yr. and terminated at 5 mo. in a spontaneous abortion of unknown cause. Second pregnancy was a stillborn breech delivery at term after a 3 day labor. Infant was large and well-developed with no obvious abnormalities and cause of death was unknown. Third, 4th and 9th pregnancies resulted in normal, full term infants who are now alive and well, but who were not available for serologic testing. Fifth pregnancy was a normal full term baby, now alive and well, who is seronegative. Sixth pregnancy was I. W., a congenital syphilitic infant and mother of the 3rd generation case in this study. Seventh and 8th pregnancies resulted in normal babies who are now alive and well and are seronegative.

For past 10 yr. she had had a chronic cough productive of yellow sputum with no fever, night sweats or weight loss. She had slight palpitation on climbing hills which had increased during past 3 yr. Otherwise, she had been well and was able to do usual hard work in the fields.

Physical findings revealed a small, poorly nourished peasant woman. Tonsils and adenoids were markedly hypertrophied. Chest was normal except for limited motion of both diaphragms. Moist rales were heard throughout both lung fields.

Chest RG revealed soft and nodular, occasionally confluent, densities throughout both lungs which were interpreted as either atypical tuberculosis or metastatic lesions from a primary undetermined source. Remote possibility of some unusual type of syphilitic involvement of lungs was also considered. No definite diagnosis could be made from films. Sputum smear and culture were negative for acid fast bacilli. On 2 occasions her blood cardiolipin-microflocculation test was 4+ with a 1:2 titre, Kline was 4+ and the Kolmer-Wassermann was doubtful. Examination of spinal fluid was refused. A diagnosis of probable latent syphilis was made.

Second Generation

I. W. was the 31 yr. old daughter of S. S. She was a normal, full term baby said to be of normal birth weight who developed severe conjunctivitis immediately after birth which cleared after 3 days without treatment. No corneal changes were noticed after this and vision was good. At age of 1 yr. she had a generalized skin eruption of unknown etiology which lasted for several months.

Some time after age of 3 yr., but still in early childhood, she again developed inflammation and discharge of eyes, following which an opacity was noted in L eye. There were remissions and exacerbations of this inflammation during the next several years, but she received no treatment. By age of 10 yr. she had severe bilateral corneal opacities which caused a moderate loss of vision.

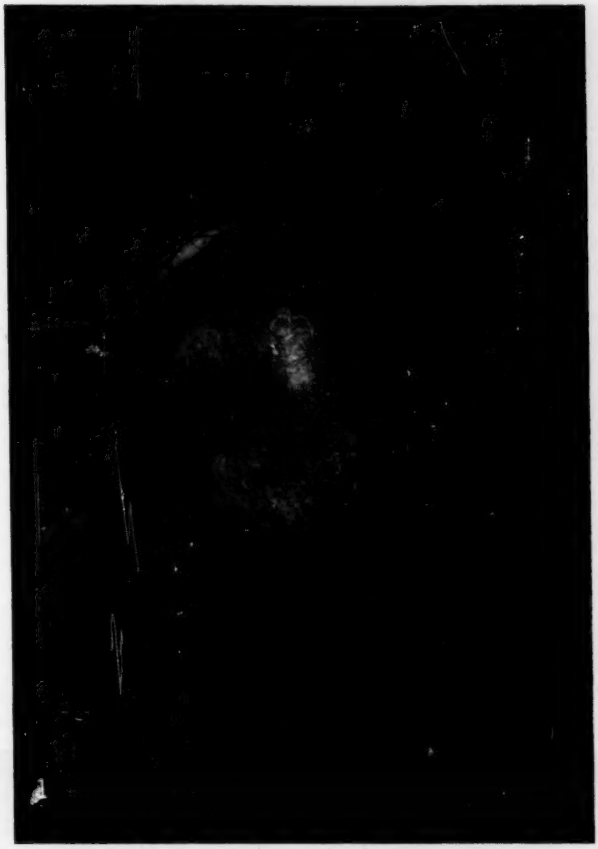

FIG. 1. A. S., first-generation syphilis patient, showing penile scar.

She had no other serious illnesses and at age of 22 yr. married a man who died 3 mo. later from acute appendicitis. No information could be obtained concerning possibility that this man might have had syphilis. There were no pregnancies from this marriage and patient denied any history of primary or secondary syphilitic lesions following that marriage.

She remained in good health until age of 26 yr. when she married her present husband. He had no history of syphilis and had repeatedly negative serologic tests for syphilis, last 2 of which were done at this clinic in course of this study.

First pregnancy was in 1949 and resulted in a normal, full term, spontaneous delivery. This baby was examined in this clinic at age of 2½ yr. at which time no signs of congenital syphilis were noted and serologic tests for syphilis were negative.

Second pregnancy was M. W. who had congenital syphilis (see below). Mother's first serologic tests were done during this pregnancy and were reported as "strongly positive."

Physical examination at the time that her baby was 3 mo. old revealed a well-developed and well-nourished Japanese woman of dull mentality with facies of congenital syphilis. She had a marked depression of nasal bridge (Fig. 2). She had severe bilateral corneal scarring (Fig. 3) and slit lamp examination confirmed an old inactive interstitial keratitis probably due to syphilis. Fundus could not be visualized but bilateral red reflexes were obtained. Hearing was normal. Upper incisor teeth, while not typically pegged or notched, were of the "screw driver" type with anteroposterior narrowing

FIG. 2. I. W., second-generation syphilis patient, showing saddle nose.

FIG. 3. I. W., corneal scarring from syphilitic interstitial keratitis.

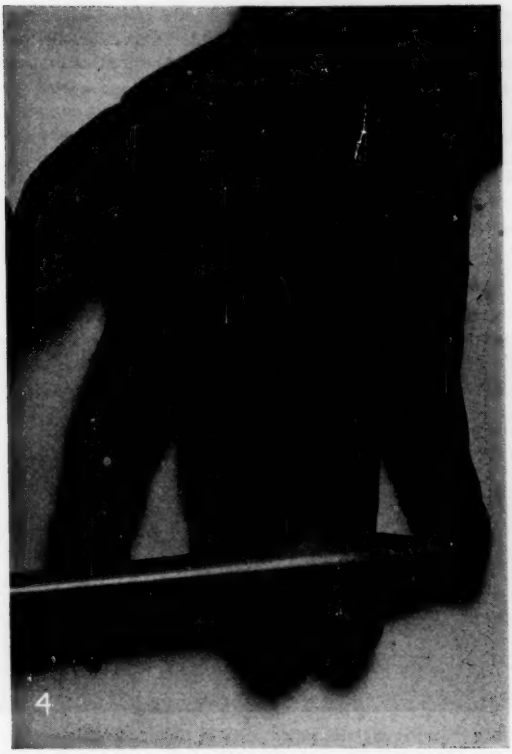

FIG. 4. M. W., third-generation syphilis patient, showing desquamation.

of the incisor borders. There were no sabre shins. The rest of physical examination was normal including the gait and the neurologic examination. Chest RG was normal.

Cardiolipin-microflocculation test was 4+, titre 1:64; Kline was 4+; and Kolmer-Wassermann was 4+, titre 1:128. Spinal fluid was clear and colorless with 26 WBC (24 lymphocytes) and 13 RBC/cmm. Spinal fluid protein was 60.0 mg./100 cc. and spinal fluid Kolmer-Wassermann was 4+ with a titre of 1:16. Colloidal gold curve was 5 5 5 4 3 2 1 000.

A diagnosis of congenital syphilis with neurosyphilis and inactive interstitial keratitis was made.

Third Generation

M. W. was second baby of this congenitally syphilitic mother who had had one previous normal pregnancy 2½ yr. before.

He was delivered spontaneously after 40 wk.' gestation and weighed 3350 gm. at birth. He was breast fed and did well until 35 days of age. At that time he became irritable and cried excessively, especially when handled. Pallor and persistent rhinitis appeared at 2 mo. of age. At 2½ mo. of age he had a febrile episode of undetermined cause which subsided spontaneously. Weight gain had been good and mother felt he was doing well. He was brought to clinic at 3 mo. of age for routine examination because of his mother's positive postpartum serologic tests for syphilis.

Physical examination revealed a well-developed and well-nourished 3 mo. old Japanese infant with a temperature of 37.4°C. who appeared markedly pale, listless and critically ill. He had snuffling respirations and cried whenever he was handled. There was brownish seborrheic scaling of scalp and periauricular regions. Palms and soles of feet were thickened, dull red and shiny with moderately

severe desquamation. There were shiny red desquamating areas around finger and toe nails. Remaining skin area was normal. There was purulent nasal discharge without rhagades or excoriation. Mucous membranes were normal. Heart and lungs were normal. Abdomen was markedly distended by a large firm liver which was palpable 5 cm. below costal margin and a hard spleen which extended 7 cm. below costal margin. There were bilateral fluctuant transilluminating testicular masses thought to be hydroceles. Baby was reluctant to move extremities and screamed whenever light pressure was applied. There were several 1 cm. cervical nodes bilaterally but no enlargement of axillary, inguinal or epitrochlear nodes. Deep tendon and superficial reflexes were normal and Moro reflex was still present.

There was a moderately severe anemia, RBC count 2.8 million cmm., Hgb. 6.4 gm./100 cc., and a leukocytosis of 23.2 thousand/cmm. Cardiolipin-microflocculation test was 3+, titre 1:256, Kolmer-Wassermann was 3+, titre 1:512. Spinal fluid was clear, colorless and contained 5 lymphocytes/cmm.; protein was 68 mg./100 cc. and Kolmer-Wassermann was 4+, no titre.

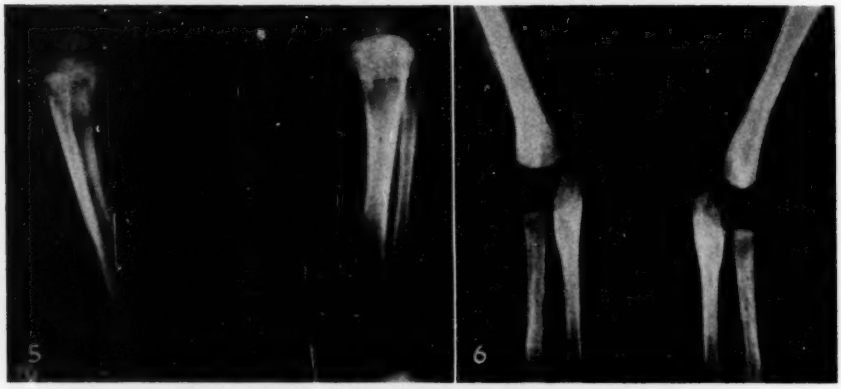

FIG. 5. M. W., third-generation syphilis patient, RG of tibia and fibula taken before treatment.
FIG. 6. M. W., third-generation syphilis, RG of elbows taken before treatment.

Chest RG was normal. RG of long bones showed moderately severe osteitis at proximal ends of ulnae and distal ends of humeri and medial borders of proximal ends of tibiae (Figs. 5 and 6). There was slight generalized periosteal elevation of most of the long bones. There were bands of increased density at distal ends of radii and ulnae with bands of decreased density just proximal to them. The changes were considered pathognomonic of congenital syphilis.

A diagnosis of congenital syphilis was made and the baby was treated with 96 hr. penicillin, 2,400,000 u., over a 2 wk. period, and made an uneventful recovery. Six months later the only remaining clinical sign was a spleen palpable 2 cm. below costal margin. RG of bones showed good healing. RBC count was 4.3 million/cmm. and Hgb. was 11.2/100 cc. Cardiolipin-microflocculation was 4+ and the Kolmer-Wassermann was negative.

DISCUSSION

According to the concepts of Fournier and Finger, as quoted from Stokes,[2] the following criteria must be met in making the diagnosis of third-generation syphilis.

"Acquired syphilis must be demonstrated in the grandmother and preferably also in the grandfather." The grandparents reported in this study both had positive serologic tests and the grandfather had a penile scar and history of venereal disease.

"Prenatal, as distinguished from acquired syphilis, must be demonstrated in the mother of the third-generation case. Acquired syphilis must be excluded in her case and the father must be proved to be healthy." The mother reported here had severe corneal scarring

with a history of eye disease in early childhood. While many other conditions such as riboflavin deficiency and tuberculosis, which are common in Japan, can give rise to corneal opacities, slit-lamp examination is a valuable aid in the differential diagnosis and in this case corroborated the diagnosis of congenital syphilis. The mother also presented the typical facies of depressed nasal bridge and abnormal teeth. Her serologic tests were strongly positive.

There is, however, a possibility that she was reinfected by her first husband on whom information is not available. Reinfection of congenital syphilitic patients has been reported but most of the early cases of congenital syphilis were diagnosed from clinical observation alone and were not substantiated by modern serologic testing so that well-documented cases are exceedingly rare.[4, 5]

Syphilis has been excluded in the father of the third generation case on the basis of negative history and repeatedly negative serologic tests and thus he cannot be considered as a source of reinfection. Extramarital relations by the mother cannot be positively ruled out although they were specifically denied. This remains the factor which can never be satisfactorily excluded and is thus common to all cases of presumed third-generation syphilis reported so far.

"There must be incontestable evidence of prenatal syphilis in the third generation." The baby reported here had classical physical signs including rhinitis, hepatosplenomegaly, bone pain, roentgenographic evidence of osteitis and periostitis and strongly positive serologic tests at the age of 13 weeks, so that there can be no question of the diagnosis.

"Manifestations must appear soon after birth in both the second and third generation." This is difficult to prove in the second-generation case reported here as the early history of the mother is vague. Her history of early skin lesions is common to many Japanese children and is probably not significant. Symptoms of interstitial keratitis appeared somewhat earlier than usual in her case. The diagnosis was easily made in her infant at the age of 13 weeks.

Summary

A family study tracing a syphilitic infection from grandparents to mother to infant is presented. Data are presented which fulfill the rigid criteria necessary for diagnosis of a case of third-generation syphilis.

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Spanish Abstract

Un Caso Probable de Sífilis Congénita a Traves de Tres Generaciones

Los autores presentan el caso de un niño de 13 semanas con sífilis congénita en cuya madre y abuelos maternos fué posible diagnosticar su origen.

Al abuelo materno, de 62 años de edad se le hizo diagnostico de sífilis por presentar historia de infección venérea, cicatriz excavada en pene y la reacción de Kolmen Wassermann con 3+.

La abuela materna dió historia de un aborto espontáneo a los 5 meses en el primer embarazo; del

siguiente nació un niño a término pero muerto después de tres días de trabajo de parto. El tercero, cuarto, quinto y noveno embarazo dieron niños sanos, a término, viven pero se desconoce su serología, con excepción del quinto niño que es negativa. Del sexto embarazo nació un niño con sífilis congénita y es la madre del enfermo, que es el motivo de este relato. El séptimo y el octavo embarazo dieron niños sanos, a término y con reacciones serológicas negativas a la sífilis. Las reacciones serológicas para lues fueron también positivas en la abuela.

La madre del enfermo padeció de lesiones oculares tempranamente en su infancia que dejaron cicatrices corneanas intensas que al examen oftalmológico se diagnosticaron como de origen luético. Ademas, tenía la facies, típica con el puente nasal deprimido y dientes anormales, sus reacciones serológicas y en líquido cefalorraquídeo fueron intensamente positivas, haciéndose el diagnóstico de sífilis congénita con neurosífilis. Tuvo dos niños en su segundo casamiento, el primero fué sano y con reacciones negativas y el segundo, que es el niño que se estudia tenía sífilis congénita.

El enfermo en cuestión nació bien pero a los 35 días se puso muy irritable y lloraba mucho, especialmente al moverlo. A los tres meses se le examinó encontrándosele rinitis, hepato y esplenomegalia, dolores óseos y roentgenologicamente habia osteoperiostitis. Sus reacciones serológicas fueron intensamente positivas a las 13 semanas de vida.

De acuerdo con los conceptos de Fournier y Finger, se deben llenar los siguientes requisitos para hacer el diagnóstico de sífilis congénita en tercera generación: 1ª.—Debe demostrarse la presencia de sífilis adquirida en la abuela y de preferencia en el abuelo también. 2°.—Se debe demostrar la presencia de sífilis en la madre pero ésta debe ser congénita y no adquirida. Esta última debe excluirse y probarse que el padre es sano. 3°.—Deben encontrarse pruebas incontrovertibles de sífilis prenatal en la tercera generación. 4°.—Las manifestaciones sifilíticas deben aparecer poco después del nacimiento tanto en la segunda como en la tercera generación.

En el caso relatado el 1° punto parece estar plenamente demostrado, el 2° no lo es satisfactoriamente, pues la madre casó dos veces y aunque el esposo del segundo casamiento y padre del enfermo no tuvo antecedentes ni reacciones luéticas positivas, del primer esposo no se supo nada sobre el particular. Tampoco se puede excluir la posibilidad de sífilis por contacto sexual extramarital aunque estos fueron negados específicamente. El 3° punto se comprobó a satisfacción pero el 4° es vago en lo referente a la segunda generación o sea la madre y plenamente seguro en su hijo.

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MEASLES ENCEPHALITIS

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THIS is a report of 35 cases of measles encephalitis treated at The Charles V. Chapin Hospital during the past 15 years (1937-1952). As this hospital treats exclusively practically all infectious diseases in Rhode Island and nearby Connecticut and Massachusetts, this should be an estimate of the incidence of such cases in this area. However, in some localities outside of Providence, the reporting of infectious diseases is not accurate and the incidence of measles encephalitis may be less than appears statistically.

HISTORY

Measles encephalitis was first described as a clinical entity in this country by Neal and Appelbaum in 1927.[1] Ford[2] added several cases of his own. Peterman and Fox[3] supplied further clinical data and the pathology of the condition was then dealt with at length by various workers.[4, 5]

Hamilton and Hanna[6] stated there was no evidence of predisposition connected with the severity of the measles infection, the age, or the sex.

Sawchuk et al.,[7] in a study of 50 cases, reported an incidence of 58% in a female with a mortality rate of 32% and Appelbaum et al.,[8] in a further survey of 74 cases, reported an incidence of 58.9% in the female with a mortality rate of 9.5%.

SYMPTOMS

Fever, headache, vomiting, irritability and convulsive seizures were by far the most common initial symptoms, varying in onset from one to six days after the appearance of the rash, the average being 3.7 days. Convulsions occurred in 20 cases and coma in 12 cases. Temperature varied from 36.7° to 41.0°C. but the majority of cases ranged in the region of 38.3° to 39.4°C.

SYMPTOMATOLOGY

The onset of encephalitis usually occurs on the third, fourth or fifth day after the rash has begun to fade and the temperature has subsided. It may occur concomitantly with or preceding the rash. The onset is sudden, the patient usually being perfectly well until the appearance of drowsiness, headache and convulsive seizures, followed by stupor. This is most often accompanied by a moderate or severe rise in temperature. Muscular rigidity and twitching may occur at this time. The stupor may be prolonged or recovery may ensue without residual symptoms, although involvement of the nervous system may become manifest on return to consciousness. A mental upset, varying from slight personality change to complete mental deterioration, occurs in a great many cases and one girl 5 years of age in this series became completely unmanageable and required institutionalization. No therapeutic measure has any effect on the course of the disease.

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The cerebrospinal fluid usually shows a pleocytosis with a preponderance of lymphocytes, normal or slightly elevated protein, and normal or moderately raised sugar content. A moderate leucocytosis, with a polymorphonuclear response, is the usual feature.

On breaking down this 15 year summary into two periods, the increasing frequency of this complication of rubeola becomes more striking.

Years	No. of Cases of Rubeola	No. of Cases of Encephalitis	Incidence
1937-1946	30,101	10 (29%)	1:3010
1947-1952 (Apr.)	20,180	25 (71%)	1:807

The increasing incidence of measles encephalitis in Rhode Island is shown graphically in chart 1 and table 1.

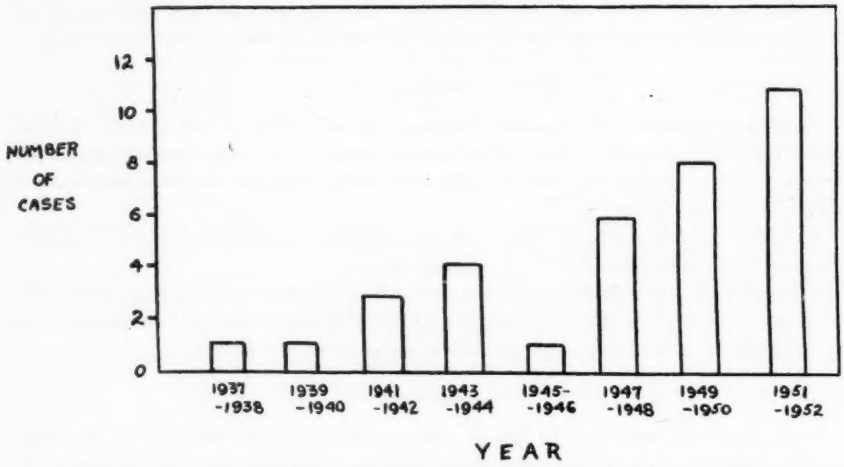

CHART 1. Increasing incidence of measles encephalitis in Rhode Island, 1937-1952.

AGE AND SEX

The age at onset of these 35 cases of measles encephalitis varied from 15 months to 29 years, with an average age of 7.6 years (chart 2). Twenty-four cases, however, occurred in the 4 to 8 year group.

Uncomplicated rubeola is not admitted to this hospital usually but 1,187 cases severe enough to require hospitalization were admitted from 1937 to April 1952. Of this number, 628 were males and 559 females, a significantly higher number of males than females ($P = .05$).

In the group of 35 cases of measles encephalitis, only 13 were males and the females numbered 22, but statistically there was no significant difference between the number of males and females in this sample ($P = .10$). On further analysis, however, the average age of male and female subjects was found to be 6.3 years and 9.2 years, respectively, and the females with measles encephalitis were significantly older ($P < .05$) on the average than males with the same complication, and significantly older ($P = .01$) on the average than females who merely contracted an uncomplicated case of rubeola.

Of 100 consecutive cases admitted with uncomplicated rubeola, no significant difference between the average age of males (5.2 years) and females (5.7 years) was found.

TABLE 1

INCIDENCE IN RHODE ISLAND

Year	No. of Cases of Rubeola	No. of Cases of Encephalitis	Incidence
1937	5,430	1	1:5430
1938	140	0	
1939	2,468	0	
1940	5,288	1	1:5288
1941	604	0	
1942	5,206	3	1:1735
1943	2,497	3	1:832
1944	6,878	1	1:6878
1945	272	0	
1946	1,318	1	1:1318
1947	5,274	6	1:875
1948	623	0	
1949	6,661	7	1:951
1950	342	1	1:342
1951	1,278	3	1:426
1952 (Apr.)	6,002	8	1:750
Total	50,281	35	Mean Incidence 1:1436

The authors' group showed a preponderance in the female of 22 of 35 cases and a mortality rate of 20% (all females) and although they concur with the finding that the severity of the rubeola bears no relationship to the onset of encephalitis, it is believed that the previous history, age and sex may be significant.

LABORATORY FINDINGS

The diagnosis was made on clinical findings alone and confirmed, in most cases, by the presence of pleocytosis in the cerebrospinal fluid. This varied from 0 to 1500

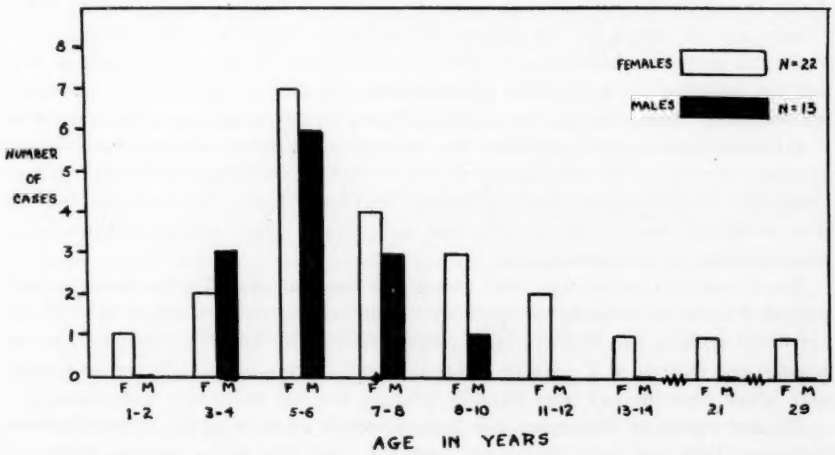

CHART 2. Distribution of 35 cases of measles encephalitis by age and sex.

cells/mm.^{3}, the cells being mainly mononuclear in type. Four cases showed less than 5 cells/mm.^{3} in the cerebrospinal fluid on the initial lumbar puncture but one of these showed 46 lymphocytes/mm.^{3} on repeat examination done on the third hospital day. Spinal fluid was not examined in two cases. The average cell count varied between 15 to 150/mm.^{3} Sugar content of the cerebrospinal fluid was normal or only moderately raised, and the protein was normal or slightly elevated.

The cell counts in 5 of the 7 fatal cases in this series were 120, 33, 2, 46 and 70/mm^3, respectively, which suggests that a low cerebrospinal fluid cell count indicates a grave prognosis.[7]

The white blood cell count varied from 4,275 to 30,400/mm^3, the majority being moderately elevated.

Mortality Rate

All of the seven deaths in this group occurred in females, who ranged in age from 15 months to 13 years.

Age	Onset of Symptoms After Appearance of Rash	Death
1. 9 yr.	4 days	3rd day
2. 12 yr.	5 "	" "
3. 7 yr.	4 "	1st "
4. 8 yr.	3 "	" "
5. 3 yr.	2 "	2nd "
6. 15 mo.	1 "	6th "
7. 13 yr.	5 "	4 hr.

It is significant that all seven fatal cases showed convulsions and coma and that although the majority of cases of measles encephalitis is in the 4 to 8 year age group, five of these cases were 7 years and over.

In the 16 cases 7 years of age and above, five died, while in the 19 cases under that age there were 2 deaths.

Previous History

The previous history in each case was reviewed in an attempt to discover some common factor to explain the older average age in the female (9.2 years), the exclusively female fatality and the reason for the majority of the deaths occurring in the age group of 7 years and over. The findings were epidemic parotitis in 10 cases, and 1 each of acute anterior poliomyelitis, questionable poliomyelitis, gross mental retardation (? cretinism), marked speech retardation in a 5 year old child, and "spinal" meningitis with convulsions.

It is considered by many authorities that meningoencephalitis occurs concomitantly with epidemic parotitis in the vast majority of cases[9–12] and the occurrence of mumps meningoencephalitis without parotid swelling has been described.[13] If one can assume this premise, it is noteworthy that 15 cases in this series had previous central nervous system involvement. Of these 15, 10 were females.

The 13 year old patient who died within four hours of admission had been perfectly well until five days following the appearance of the rash, when she suddenly had repeated convulsive seizures two hours prior to hospitalization. Her history showed seizures unaccompanied by fever at the age of 1 year and "spinal" meningitis at the age of 6 years, since which time she had been mentally retarded and had attended a special school.

The case reports of 100 consecutive cases of rubeola admitted to this hospital between November 1951 and June 1952 were examined. Only 8% had a previous history of

epidemic parotitis and no other evidence of central nervous system involvement was found. This group ranged in age from 8 months to 51 years and in the 8 cases having a history of epidemic parotitis, the ages were from 6 to 19 years, and 6 of them were males.

Discussion

The reason for the increase in the incidence of measles encephalitis seems to be obscure.

The older average age of females is another vexing problem. Whether previous central nervous system damage is a possible prognostic feature seems worthy of further study.

That the majority of deaths in this series occurred in those 7 years of age and over might suggest that the longer period of time after previous invasion of the central nervous system by epidemic parotitis or some other disease is a factor.

Gamma globulin in attenuating dose is efficacious in reducing the incidence of other secondary complications. Janeway[14] reported an incidence of encephalitis of 0.4% in one group, using concentrated human serum gamma globulin, which resulted in a modified form of the disease, whereas those showing no modification had complications in 5.5%. The same report mentions one case of mild measles encephalitis with complete recovery following concentrated human gamma globulin, but no apparent benefit could be ascribed to this form of therapy.

Measles encephalitis following an attenuating dose of gamma globulin has been reported.[15] This child, too, made a probable complete recovery within one month of discharge from the hospital.

Both these cases were relatively mild in nature and probably recovered completely. Whether the outcome would have been more serious without the attenuating therapy is open to conjecture. Further study with a larger series of cases is needed to answer this point and until then it would seem reasonable to give gamma globulin in attenuating doses to all patients, particularly female, with a previous history of central nervous system involvement.

Summary

Thirty-five cases of measles encephalitis over a 15 year period are reviewed. The rising incidence of this complication is suggested. The older average age and the mortality rate occurring in females is noted, and a concept based on previous central nervous system involvement to account for this is presented. The use of gamma globulin is discussed.

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SPANISH ABSTRACT

Encefalitis Sarampionosa

Los autores hacen una revisión de 35 casos de encefalitis sarampionosa ocurridos durante un periodo de 15 años, de 1937 a 1952, y reportan los siguientes aspectos interesantes:

Se presentaron 35 casos de encefalitis en 50.281 enfermos de sarampión o sea una incidencia promedio de 1 por cada 1436 sarampionosos.

La incidencia de la encefalitis ha venido aumentando en los últimos años, de 1937-1946, en 30.101 casos, fué de 29% y entre 1947-1952, 20.180 casos, alcanzó el 71%.

El 68.5% de los casos de encefalitis ocurrieron entre los 4 y 8 años de edad, el promedio fué de 7.6 años.

Estadísticamente no se encontró diferencia significante entre el número de niños y niñas que tuvieron encefalitis. La edad promedio de los enfermos fué de 6.3 años para los hombres y de 9.2 para las mujeres, estas últimas, como promedio, tenían mayor edad, significativamente, que los hombres con dicha complicación y que las mujeres que tuvieron sarampión no complicado. En 100 casos consecutivos de sarampión sin encefalitis no se encontró diferencia significativa entre las edades de los hombres y mujeres, 5.2 y 5.7 años respectivamente.

Los síntomas mas frecuentes fueron fiebre, cefalea, vómitos, irritabilidad y convulsiones. Se iniciaron entre el 1° al 6° día de la aparición de la erupción. En el 57% de los enfermos hubo convulsiones y en el 34% coma.

El diagnóstico se hizo por la clínica y el examen del líquido cefalorraquídeo. Hubo pleocitosis de cero a 1500 celulas por milímetro cúbico, siendo mononucleares las celulas predominantes. Cuatro casos tuvieron menos de 5 celulas inicialmente, en uno de ellos subieron a 46, todos linfocitos, al tercer día. La pleocitosis promedio fué de 15 a 150. La glucosa y las proteínas del líquido estaban normales o ligeramente aumentadas. Los leucocitos sanguíneos variaron de 4.275 a 30.400, la mayoría tuvo ligera leucocitosis.

Hubo 7 muertes en los 35 casos de encefalitis, y ocurrieron exclusivamente en mujeres y todas presentaron convulsiones y coma. Cinco de ellas se presentaron en el grupo de 7 años para arriba, dando una mortalidad de 31%, y 2 en el grupo de menos de 7 años, dando mortalidad de 10%.

Haciendo un intento para descubrir algún denominador común que explicara la frecuencia de la encefalitis en una edad promedio mayor en las mujeres (9.2 años), la mortalidad exclusivamente entre ellas, y la razón por la que la mayoría de las muertes ocurrieron en el grupo de 7 años para arriba, se hizo una revisión de los antecedentes patológicos de los casos y se encontró que 10 enfermos habían padecido parotiditis epidémica, un caso poliomielitis anterior aguda, otro mas, dudoso, un caso de retardo mental, lenguaje retardado intenso en otro, y uno mas con meningitis. Aceptando la premisa de que en la gran mayoría de casos de parotiditis se presenta meningoencefalitis concomitantemente, en 15 casos de esta serie de encefalitis sarampionosa (43%) existiría un ataque previo al sistema nervioso central y 10 de ellos (66%) eran mujeres. Solo 8 de 100 casos de sarampión sin encefalitis presentaron historia de parotiditis y sus edades oscilaron entre 6 y 19 años y 6 de ellos eran hombres.

Parece pues que no hay duda que la frecuencia de la encefalitis sarampionosa esta en aumento, y queda sin contestación la pregunta de si la quimio y antibióterapia, reduciendo la alta mortalidad previa debida a infecciones secundarias, no sean las causantes de ello. La posibilidad de que una lesión

previa del sistema nervioso central tenga valor pronóstico debe estudiarse mas y comprobarse por otras revisiones. Otra problema es la explicación de la edad mayor en las mujeres con encefalitis.

Es posible que la mayor mortalidad por arriba del 6° año sea debido a que se tenga un período mas largo de tiempo para invasiones previas del sistema nervioso central ya por parotiditis u otro padecimiento.

La posibilidad de que la gammaglobulina humana en dosis atenuantes pueda prevenir la encefalitis sarampionosa así como reducir la incidencia de complicaciones secundarias, aun se desconoce, y hasta que se sepa este punto será razonable atenuar todos los casos tan pronto como sean expuestas al sarampión, particularmente mujeres con antecedentes previos de lesión del sistema nervioso central.

Charles V. Chapin Hospital

REPORT OF THREE CASES OF IDIOPATHIC FAMILIAL HYPERLIPEMIA: USE OF ACTH AND CORTISONE

By ALBERT L. GASKINS, M.D., ROLAND B. SCOTT, M.D., AND ALTHEA D. KESSLER, M.D.
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IDIOPATHIC hyperlipemia is a rare condition characterized by the following features: milky serum, marked increase in blood lipids especially neutral fat, hepatosplenomegaly, xanthomatous nodules of the skin and mucous membranes of the mouth, lipemia retinalis and recurrent abdominal pain. Regression of symptoms and decrease of blood lipids, though still above normal values, have been noted on low fat diets. Apparently the condition may be asymptomatic in individuals showing a lesser degree of lipemia as in parents and siblings of some of the reported cases.

Previously reported cases with clinical findings are listed in table 1. The present authors wish to report three cases of idiopathic hyperlipemia in siblings.

Pathologic examinations have been confined mostly to biopsy material since only one reported case[7] has come to autopsy. Large macrophages containing fat droplets may be found in the skin lesions, liver, spleen and bone marrow. Thannhauser[15] states that all demonstrable pathology is the result of fat storage by the reticuloendothelial cells secondary to excess of blood lipids. He, therefore, describes the condition as idiopathic hyperlipemia with secondary eruptive xanthomatosis and hepatosplenomegaly.

CASE REPORTS

Case 1: P.P., a 3½ yr. old Negro male with no complaints, was admitted to Freedmen's Hospital for study because hyperlipemia had been discovered on a blood specimen drawn for routine studies 2 yr. previously.

Birth and development had been normal. He ate an ordinary mixed diet and presented no feeding difficulties. Only previous illnesses were a cellulitis of face at 1½ yr. of age, and several attacks of impetigo of legs in past 2 yr.

Two brothers with lipemia were admitted for study at the same time. Father was being treated for bronchiectasis. Mother, a sister and a brother were all in good health. Three siblings had died in infancy, causes being unrelated to condition under discussion.

Patient was a well developed, healthy boy. Weight: 15.9 kg. Height: 101 cm. There was a small abscess of R axilla. Healed depigmented areas from a recent impetigo were present over anterior tibial regions. No other skin lesions were present. Abdominal organs were not palpable. Retinal vessels presented a creamy white appearance.

Hospital course was uneventful. Axillary abscess healed following incision. He received an ordinary ward diet. Penicillin was only medication given.

Case 2: L. P. was a 13 yr. old male whose only complaint was chronic ulceration of legs for 3 yr. Ulceration followed recurrent bouts of impetigo. One year before admission skin grafting of ulcers had been done at another hospital. Following this R leg had healed but grafts had not taken on L leg.

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TABLE 1

REPORTED CASES OF IDIOPATHIC HYPERLIPEMIA

Author	Age of pt.	Familial incidence	Nutrition	Abdominal pain	Xanthomatosis	Hepatosplenomegaly	Lipemia retinalis	Improved on low fat diet	Microscopic evidence of abnormal fat storage			
									Skin	Liver	Spleen	Marrow
Burger[1]	11		fair	−	+	+	+	+				
Opitz[2]	12		poor dwarfed	−	−	+		+				
Franklin[3]	5		poor	−	−	+					−	
Bernstein[4]	6		fair	−	+	+	+	+				
Holt[5]	11	+	poor	+	−	+	+	+	−			
Chapman[6] and Goodman[7]	1	−	poor	+	+	+	+	+	+	−	+	+
Levey[8]	8½	+	fair	+	−	+	+	+				
Bruton[9]	2	+	good	+	+	+	+	+		+		+
Shore[10]	28		good	+	−	−		+				−
Bloomfield[11]	28		obese	+	+	−						
Grossman[12]	55			+	−	liver + spleen −	+	+				
Hopgood[13]	26	−	good	+	+	+		+				
Harslof[14]	16	−	obese dwarfed	−	−	+	+	+				−

Birth and development had been normal. Only other illness was an eye injury requiring operation at 1½ yr. of age. Hyperlipemia had been discovered 9 yr. before present admission on a routine blood examination.

He was well nourished and developed. Weight: 35.4 kg. Height: 139 cm. There was a 2.5 transverse scar below L lower lid. Fundoscopic examination showed lipemia retinalis (Fig. 1). Liver was palpated at costal margin; spleen was 1 fingerbreadth below costal margin. There was a healed donor graft site on L thigh. Several scars were present on both lower legs including a healed graft over lower ⅓ of R tibial area. There was a granulating ulcer measuring 7.5 by 11.8 cm., covered by a film of yellow pus, over the lower left tibial area (Fig. 2).

Cortisone acetate* was given intramuscularly, 40 mg. every 6 hr. for 24 hr., then 50 mg. twice daily for 9 days. He received an ordinary ward diet except during cortisone therapy when a low sodium diet was given. He remained asymptomatic except for leg ulcers which showed no improvement.

Case 3: J. P. was an 18 yr. old male whose only complaint was recurrent ulcers of legs for 11 yr.

Birth and development had been normal. During infancy he had occasional vomiting episodes but since that time there had been no gastrointestinal symptoms. His diet had not been restricted. At 7 yr. of age he was hospitalized elsewhere for an eye disorder, nature of which is not known. Hyperlipemia was discovered at that time.

He was well nourished and well developed. Weight: 53.6 kg. Height: 166 cm. Fundoscopic examination showed lipemia retinalis. Liver edge was at costal margin. Spleen was not palpable. There were 3 small and one large ulcer over middle third of L tibia. Similarly, there were 2 small

* Supplied by Merck & Co., Inc., Rahway, N.J.

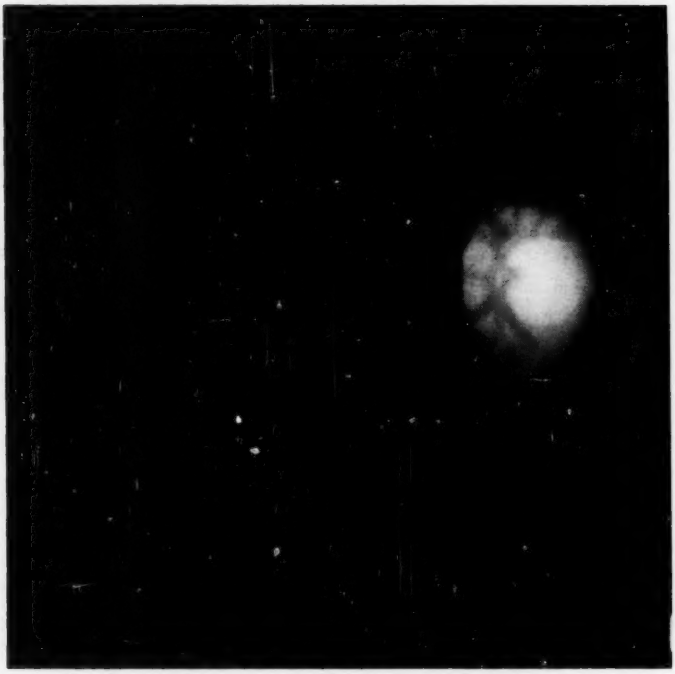

FIG. 1. Retina (L. P.). Note light appearance of vessels.

and 2 large ulcers over middle third of R tibia. Bases of ulcers were filled with fresh granulation tissue showing no evidence of infection. There were no other skin lesions.

Adrenocorticotrophic hormone* 25 mg. in 500 cc. of 5% glucose in water, according to method of Renold,[16] was administered intravenously daily for 10 days. Patient remained asymptomatic except for ulcers which showed no change.

Laboratory Data: Blood serum of all 3 patients showed a milky white supernatant layer.

Blood lipid values on patients, parents and one sibling are shown in charts 1 to 4. Total lipids and especially neutral fat were markedly elevated in all 3 patients, and to a lesser degree in mother. Father and sister had normal lipid levels.

Sickling of erythrocytes was demonstrated in 3 patients and father but not in mother or sister. None of them had a history of anemia. Hemoglobin, RBC counts and bilirubin determinations were all within normal limits. Blood specimens from 2 older patients were submitted to Dr. Karl Singer, Michael Reese Hospital, Chicago, for determination of fetal hemoglobin. No alkali-resistant hemoglobin was found.

Aspirated sternal marrow showed a preponderance of normoblastic elements. Large vacuolated foam cells were unevenly distributed throughout the marrow. The appearance of marrow was unchanged after treatment.

Biopsies of leg ulcers were classified as chronic pyogenic ulcers with no distinctive features. There was chronic granulomatous ulceration of skin with an abundance of richly vascularized connective tissue infiltrated focally by leucocytes of all types.

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* Supplied by The Armour Laboratories, Chicago.

FIG. 2. L. P. Leg ulcers.

Punch biopsies of liver on 2 older boys showed, both before and after treatment, coarsely granular cord cells with a number of fat vacuoles and scattered multinucleated giant cells.

On ordinary ward diets respiratory quotients were as follows: P.P.—.81; L.P.—.86; J.P.—.94. Other laboratory studies which were within normal limits included hemograms, urinalyses, urine urobilinogen, stool examination for fat, serologic test for syphilis, galactose tolerance test, plasma protein, NPN, blood sugar, prothrombin, ECGs and RGs of chest, skull and long bones.

Prompt decrease in circulating eosinophils occurred in both patients receiving hormone therapy. This was maintained for duration of therapy in patient receiving cortisone. In the patient receiving ACTH, eosinophils rose almost to pretreatment levels by 8th day.

These 2 patients were readmitted 6 mo. later for another course of hormone therapy. Although they had been taking a low fat diet, blood lipid levels were essentially unchanged. Leg ulcers were healed on older patient and somewhat improved on younger. Second course of treatment was exactly like the first in each case. Immediately following second course, plasma lipid levels were markedly increased in the patient receiving cortisone, but moderately decreased in the patient on ACTH (charts 1-4).

DISCUSSION

Thannhauser[15] classifies the disorders of lipid metabolism as follows:

1. Alimentary hyperlipemia—found in normal individuals 3 to 7 hours after ingestion of a high fat meal.

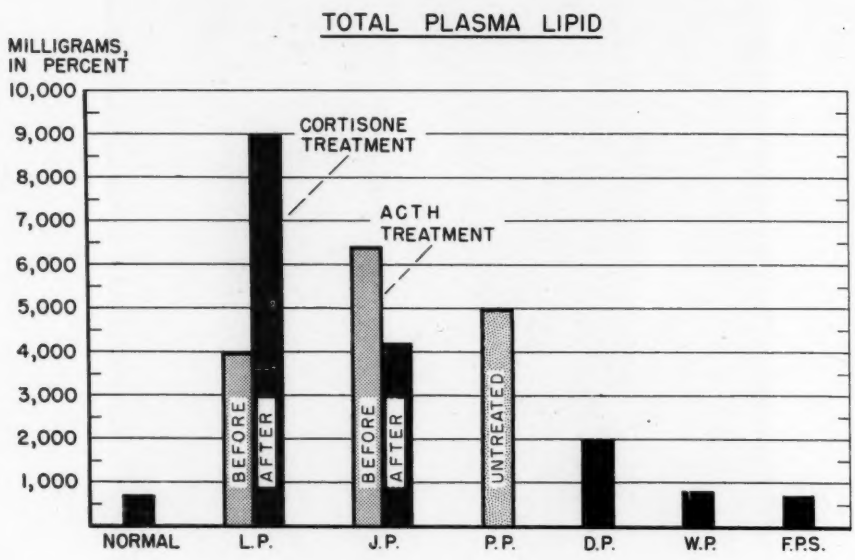

CHART 1

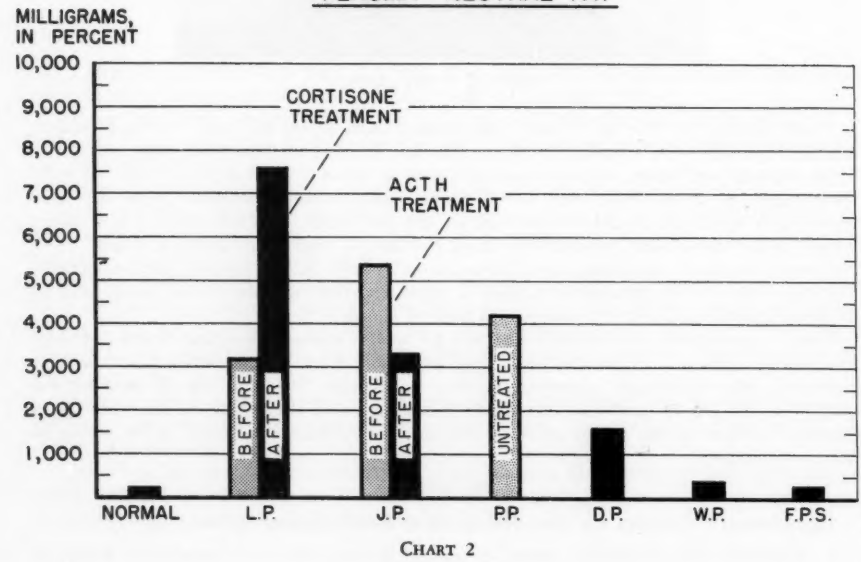

CHART 2

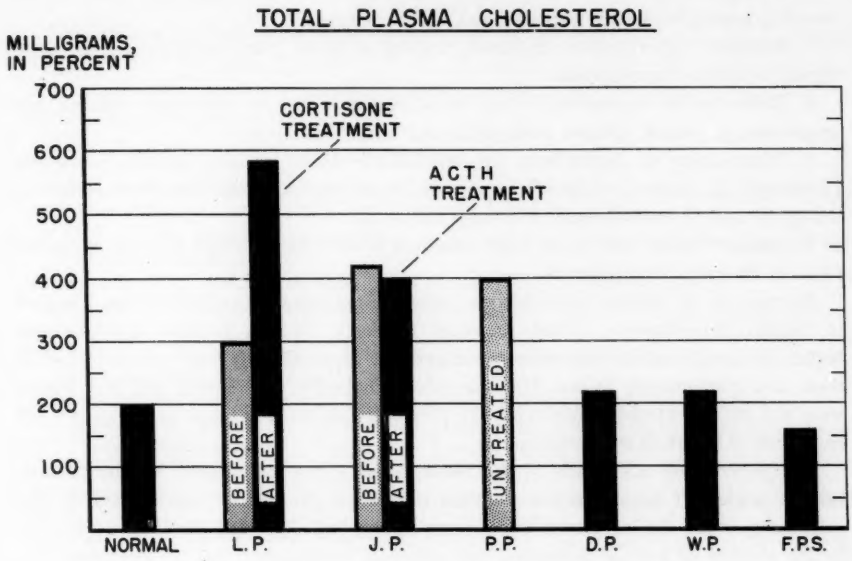

CHART 3

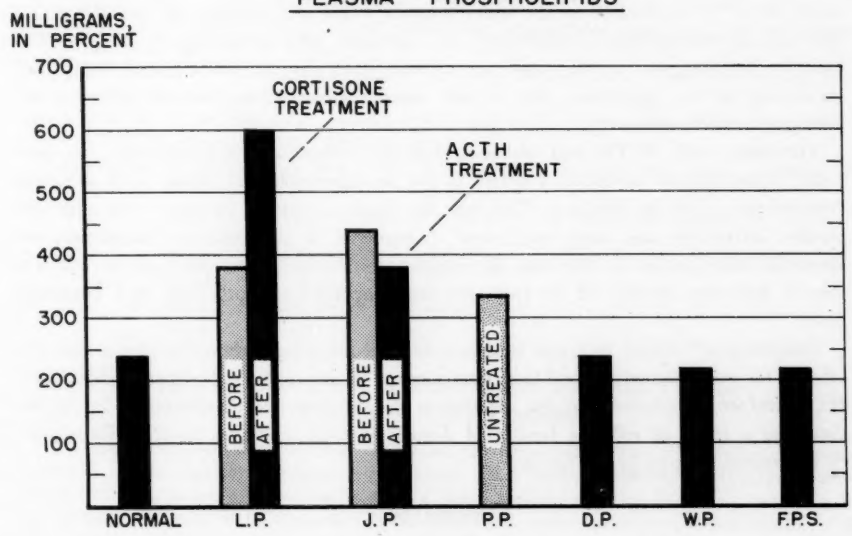

CHART 4

2. Transport hyperlipemia—increased mobilization of fat from the tissue depots found in anemia, leukemia, starvation and lipoid nephrosis.

3. Retention hyperlipemia—defective removal of lipids from the blood by the tissue depots, idiopathic hyperlipemia.

4. Defective fat combustion in the liver—found in poorly controlled diabetes, glycogen storage disease, chronic pancreatitis and biliary cirrhosis.

5. Disturbances of intracellular fat metabolism—Hand-Schüller-Christian syndrome, Niemann-Pick disease and Gaucher's disease. Hyperlipemia is not a constant feature in this group and, if present, does not involve neutral fat.

Thannhauser states that in no other condition is there such marked increase in neutral fat as in idiopathic hyperlipemia.

All three of the patients reported here presented the necessary criteria for the diagnosis of familial hyperlipemia, namely, familial incidence, lipemia retinalis and increased blood lipids with marked elevation of neutral fat. Hepatomegaly was present in two of them and splenomegaly in one. However, abdominal crises were absent and skin lesions were not of the xanthomatous type. Of previously reported cases only Holt's patient[5] had a similar but much smaller ulcer.

The presence of sickle cells in the blood posed a problem because of the possible role of sickle cell disease in the causation of part of the clinical picture, namely, the splenomegaly and the leg ulcers. The authors believe that sickle cell anemia was excluded by the absence of anemia, hemolysis and abnormal hemoglobin, and the demonstration of the sickling trait in only one parent.

Singer[17, 18] has demonstrated an alkali-resistant hemoglobin similar to fetal hemoglobin in persons with active sickle cell disease but not in those with the asymptomatic sickling trait. Neel,[19, 20] in studies on the inheritance of sickle cell anemia, has postulated that the sickling phenomenon is transmitted by a dominant gene producing the asymptomatic trait in heterozygous persons and the active disease in the homozygous individual. According to this hypothesis, only if both parents show sickling can they produce offspring with sickle cell anemia.

Treatment with ACTH and cortisone was undertaken on the assumption that idiopathic hyperlipemia represents a defect of the reticuloendothelial system with abnormal metabolism of fat by the liver. This was the theory advanced by Holt.[5] His case was studied intensively and there was found no evidence of abnormal fat combustion nor abnormal mobilization of fat from the depots. He concluded that the hyperlipemia was due to defective removal of fat from the blood by the liver, probably on a hormonal basis.

Thannhauser[15] found in tracer studies with fat-containing radioactive iodine that the labeled fat was retained in the blood stream much longer in the hyperlipemic individual. He, therefore, concluded that the disorder is due to defective deposition of fat in the tissues as a result of either a functional disorder of the capillaries or of a disturbance of the enzyme system in the fat depots.

Summary

Three cases of idiopathic hyperlipemia with associated sicklemia in siblings are reported. One case was treated with ACTH and one with cortisone neither of which had any apparent lasting effect upon the disease.

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SPANISH ABSTRACT

Reporte de Tres Casos de Hiperlipemia Idiopática Familiar: Uso de ACTH y Cortisona

La hiperlipemia idiopática es un padecimiento raro caracterizado por: suero lechoso, aumento marcado de los lípidos sanguíneos especialmente grasa neutra, hepatoesplenomegalia, nódulos xantomatosos de la piel y membranas de la boca, lipemia retiniana y dolor abdominal recurrente. Se ha apreciado regresión de los síntomas y disminución de los lípidos sanguíneos, aunque por arriba de los valores normales, con la prescripción de dietas pobres en grasa. Aparentemente el trastorno puede ser asintomático en individuos que muestran un grado ligero de lipemia como en los padres y hermanos de algunos de los casos reportados.

Los exámenes patológicos se han reducido generalmente a material de biopsia pues sólo un caso

ha sido autopsiado. Pueden encontrarse grandes macrófagos conteniendo gotas de grasa, en las lesiones de la piel, hígado, bazo y médula ósea. Thannhauser afirma que todo el cuadro patológico es resultado del almacenamiento de la grasa por las células reticuloendoteliales, secundario a un exceso de lípidos sanguíneos y por lo tanto describe este trastorno como hiperlipemia idiopática con xantomatosis eruptiva y hepatoesplenomegalia secundarias.

Los autores añaden tres casos a los catorce reportados en la literatura; todos ellos presentaron cuadros diagnósticos característicos de hiperlipemia familiar; incidencia familiar, lipemia retiniana, lípidos sanguíneos aumentados, con elevación marcada de la grasa neutra. La hepatomegalia estaba presente en dos de ellos y la esplenomegalia en uno. Sin embargo, no presentaron crisis abdominales y las lesiones dérmicas no eran del tipo xantomatoso. Además, los tres casos presentaron eritrocitos falciformes pero sin signos de anemia.

Uno de los casos fue tratado con ACTH y otro con Cortisona, ninguno de los cuales tuvo efecto duradero aparente sobre la enfermedad.

Sixth and Bryant Streets

PUBLIC HEALTH ASPECTS OF PROBLEMS OF CURRENT INTEREST IN NEONATAL PEDIATRICS

By LEONA BAUMGARTNER, M.D., PH.D.
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THE known statistical facts regarding the incidence, morbidity or mortality of a given condition or set of conditions is the basis from which the public health official often first views a problem. I shall therefore review the salient facts regarding infant and fetal mortality, using the most recent national figures whenever available and, when not, relying on those available from large population groups. Selected figures from hospital populations may often be built on more reliable basic data than those obtained from the larger population groups for which information usually is secured from the confidential reports filed by physicians with birth and death certificates. The latter are valuable nevertheless in trying to secure the over-all picture and in covering as wide a segment of the population as possible. They also have the virtue of not being subject to the statistical defects related to the selected groups found in hospital populations.

The facts the over-all statistics show are simple ones and are summarized in the following statements. The data upon which they are based are found in the accompanying tables and charts. National figures are quoted unless otherwise noted.*

FACTS RELATED TO INFANT AND NEONATAL MORTALITY

1. Infant mortality has been reduced two-thirds since 1915. The largest drop—over 80%—is among those infants surviving the first month. The next is the 52% drop in the neonatal rate, and the least is the 31% drop in deaths in the first day (chart 1 and table 1).

2. Infant and neonatal mortality rates have dropped more rapidly since 1935 than in years before then (chart 1 and table 1).

3. Wide variations in the rates exist in urban and rural areas and in different economic groups. As the brochure accompanying a recent nation-wide study of child health (American Academy of Pediatrics in cooperation with the Children's Bureau and the Public Health Service) aptly said,[1] "A child's chances of survival depend largely upon where he lives and the circumstances of his parents."

The presence of so many of the nation's children in the families of lower income (43% in families with incomes of less than $60 a week) and the tendency of the families with more children to have lower incomes complicate the problem of securing good medical care for mothers and infants. The concentration of physicians in urban areas creates other problems in further reducing mortality rates.

4. Mortality rates for white and nonwhite infants are decreasing by about the same

From the New York City Department of Health, New York City.

Based on discussion presented at the Areal Meeting of the American Academy of Pediatrics, Washington, D.C., May 22, 1952.

(Received for publication Sept. 5, 1952.)

* All national figures are those available through the publications of the National Office of Vital Statistics and the Children's Bureau.

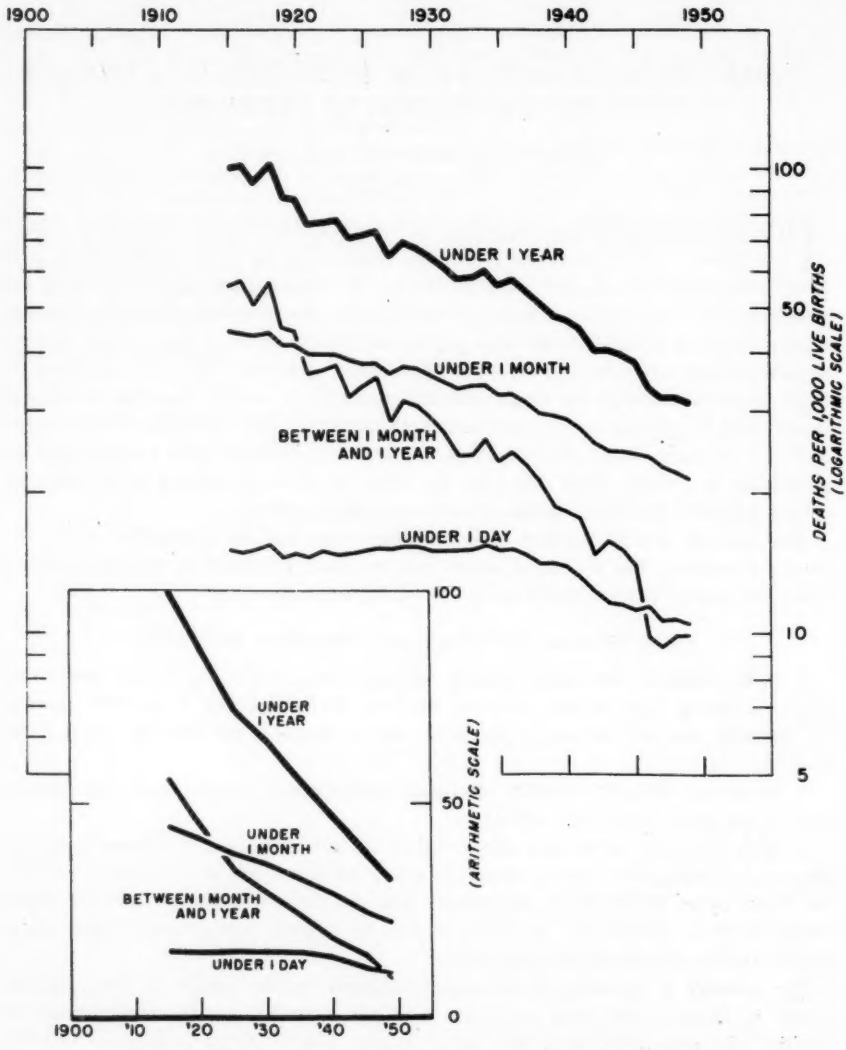

CHART 1. Infant mortality, 1915-1949 (U.S. Birth Registration Area).

percentage, but the greater risk for a nonwhite baby has changed little. In 1949 it is still 47.3 per 1000 registered live births for the nonwhite compared to 28.9 for the white.

5. The well-known differences in neonatal rates for the sexes with the relatively greater rates for males persist.

HOSPITAL BIRTHS

There has been a phenomenal increase in the percentages of births occurring in hospitals, from 37% of all registered births in 1935 to 87% in 1949. There are, however,

TABLE 1

INFANT MORTALITY RATE: UNITED STATES, 1915–49
BY AGE AT DEATH

Year	Rate per 1,000 registered live births		
	Under 1 Yr.	Under 1 Wk.	Under 1 Mo.
1949	31.3	18.3	21.4*
1948	32.0	19.0	22.2
1947	32.2	19.2	22.8
1946	33.8	20.1	24.0
1945	38.3	19.7	24.3
1944	39.8	20.0	24.7
1943	40.4	19.9	24.7
1942	40.4	20.8	25.7
1941	45.3	22.3	27.7
1940	47.0	23.2	28.8
1939	48.0	23.8	29.3
1938	51.0	23.7	29.6
1937	54.4	24.7	31.3
1936	57.1	25.8	32.6
1935	55.7	25.5	32.4
1934	60.1	26.5	34.1
1933	58.1	26.3	34.0
1932	57.6	26.1	33.5
1931	61.6	26.4	34.6
1930	64.6	27.2	35.7
1929	67.6	28.0	36.9
1928	68.7	28.2	37.2
1927	64.6	27.5	36.1
1926	73.3	28.3	37.9
1925	71.7	28.2	37.8
1924	70.8	28.5	38.6
1923	77.1	28.5	39.5
1922	76.2	29.0	39.7
1921	75.6	28.6	39.7
1920	85.8	29.2	41.5
1919	86.6	28.7	41.5
1918	100.9	30.5	44.2
1917	93.8	29.8	43.4
1916	101.0	30.2	44.1
1915	99.9	30.1	44.4

* In accordance with the new classification procedures this 1949 rate is for "under 28 days." This rate would be increased less than 1% if the 1949 data had been tabulated for the age grouping used for 1948 and earlier years.

Source: Children's Bureau.

wide variations. Rural areas in some of the southern states still have as high as 67% of deliveries of Negro mothers attended by indigenous and often untrained midwives. Urban areas, of course, have the larger percentage of hospital births, 94% in 1949 compared to 76% in the nonurban area. There are geographic differences, too. In five states, all southern, one half or more of all births are still outside the hospital. The general increase in hospital births makes certain educational and standard setting activities more effective since more physicians responsible for medical care before, during and after delivery can now be more easily reached by such programs.

Causes of Deaths

A study of causes indicates where progress is being made (table 2). From 1936 to 1948, infant deaths under one week of age from all causes decreased 26%. The rate

TABLE 2

Deaths and Death Rates under 1 Week of Age for Selected Causes and Percentage of Deaths by Cause: United States, 1936 and 1948

(Exclusive of fetal deaths. Rates per 1,000 live births)

Cause of Death (Fifth Revision of International List)		No.		Rate		Per Cent*	
		1948	1936	1948	1936	1948	1936
All causes		66,793	55,210	18.9	25.7	100.0	100.0
Premature birth	159	35,233	28,974	10.0	13.5	52.7	52.5
Injury at birth	160	11,487	8,860	3.2	4.1	17.2	16.0
Congenital malformations	157	7,587	5,524	2.1	2.6	11.4	10.0
Other diseases peculiar to early infancy	158, 161	8,107	5,285	2.3	2.5	12.1	9.6
All other causes		4,379	6,567	1.2	3.1	6.6	11.9

* Per cent of all deaths under 1 wk. of age.

Source: National Office of Vital Statistics.

associated with premature birth as a cause of death was down less than one third (26%), injury at birth down 22% and congenital malformations down only 19%. The great need for better practice in and more knowledge concerning the prevention of the non-infectious causes of infant mortality is obvious.

The outstanding problem in the infant and neonatal mortality picture today is that of the deaths associated with premature birth. In 1949 nearly 40% of all infants' deaths and 60% of all neonatal deaths were attributed to this condition.

Fetal Deaths

Deaths in viable fetuses constitute a challenging and less often discussed problem in the saving of lives of infants. The pediatrician has usually considered a stillbirth or, as it is now more properly designated, a fetal death as a matter of no concern to him. Even the physician who delivers the fetus and the pathologist have tended to pay scant attention to this problem. Yet unnecessary deaths before term are as important to families and to our society as are deaths occurring shortly after a live birth. Fetal deaths may also be an important measure of medical skill. True, reductions in prenatal syphilis, better obstetric care during pregnancy, and the increased standard of nutrition and living have helped

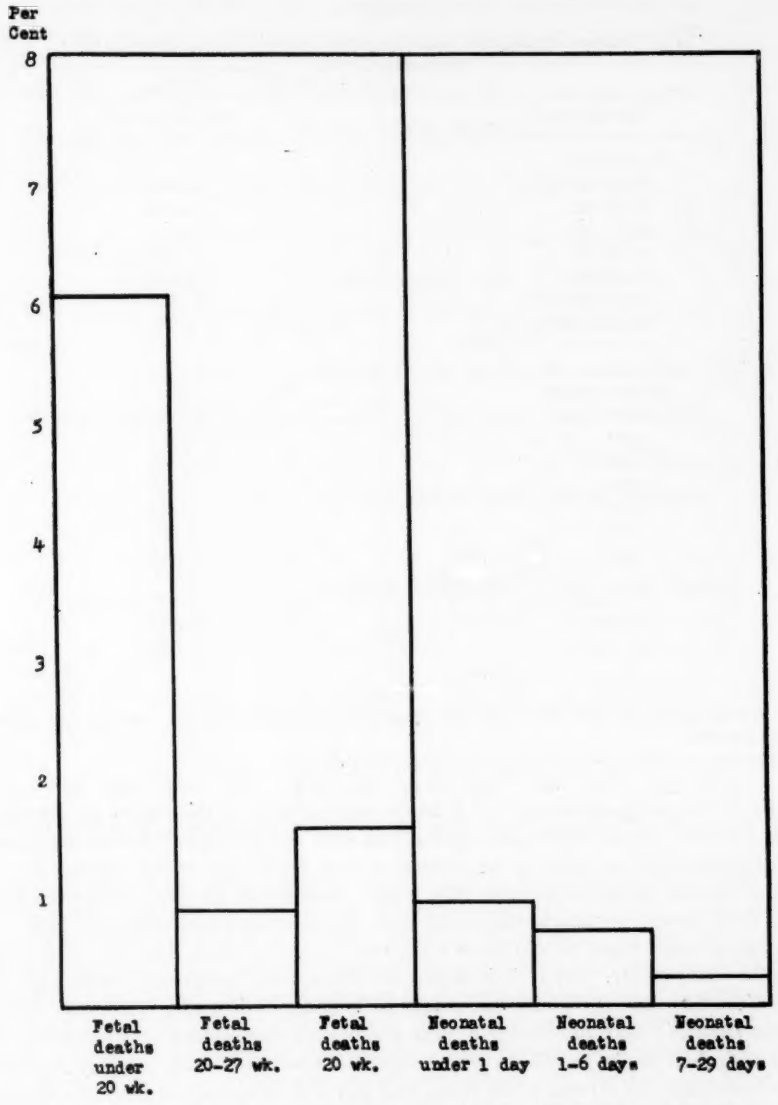

CHART 2. Proportion of known pregnancies terminating in fetal and neonatal deaths, New York City, 1949.

reduce the fetal mortality rate but careful studies of the problem and all-out attacks on it are still to be widely developed.

The problem is an enormous one and the extent of it is not even known in most communities because of the inadequate reporting (table 3). In New York City, a concerted effort has been made over the last 15 years to get all the products of conception reported

TABLE 3

FETAL DEATHS (STILLBIRTHS) AND NEONATAL DEATHS: UNITED STATES, 1949
BY AGE AT DEATH

Age at death	No. of deaths	
Fetal deaths		
Under 20 wk.*	10,940	
20–27 wk.	13,752	
28–31 wk.	8,155	
32–35 wk.	7,892	
36–39 wk.	8,340	
40 wk. and over	23,507	
Age not stated	9,903	
Total		82,489
Neonatal deaths		
Under 1 day	37,259	
1 day	11,152	
2 days	7,386	
3 days	3,953	
4 days	2,320	
5 days	1,780	
6 days	1,324	
7–13 days	5,471	
14–20 days	3,328	
21–27 days	2,353	
Total		76,326

* Almost exclusively from New York City, where reporting is probably more complete than for rest of the country.

Based on materials from the National Office of Vital Statistics.

(chart 2). These figures are believed to be the most complete in the country yet even here there is evidence of an under-reporting of at least 44% of fetal deaths.[2] An increased number of communities are studying the problem of fetal deaths. The recent adoption of uniform definitions should make more valid studies possible.[3] In the past, conclusions have often been drawn and comparisons made from incomplete and noncomparable data.

A special word might be said about early fetal deaths, i.e., those during the first 12 or even 20 weeks of life. Very little is known of the amount of pregnancy wastage here. In New York City there is evidence that at least 67% of deaths occurring in this early period are not reported.[2] Rock and Hertig in many studies have shown that a large proportion of these early fetal deaths are due to gross errors in development which preclude and even make undesirable the survival of the fetus. This may well be nature's method of disposing of the biologic sport. It is certainly a problem which awaits further elucidation.

PERINATAL MORTALITY

The further study of both fetal and neonatal mortality rates indicates that to consider these rates independently is unsound. Consider, for example, the decline in both rates in New York City where reporting is probably sufficiently adequate to study the problem for the 12 year period 1938 to 1949 (chart 3).

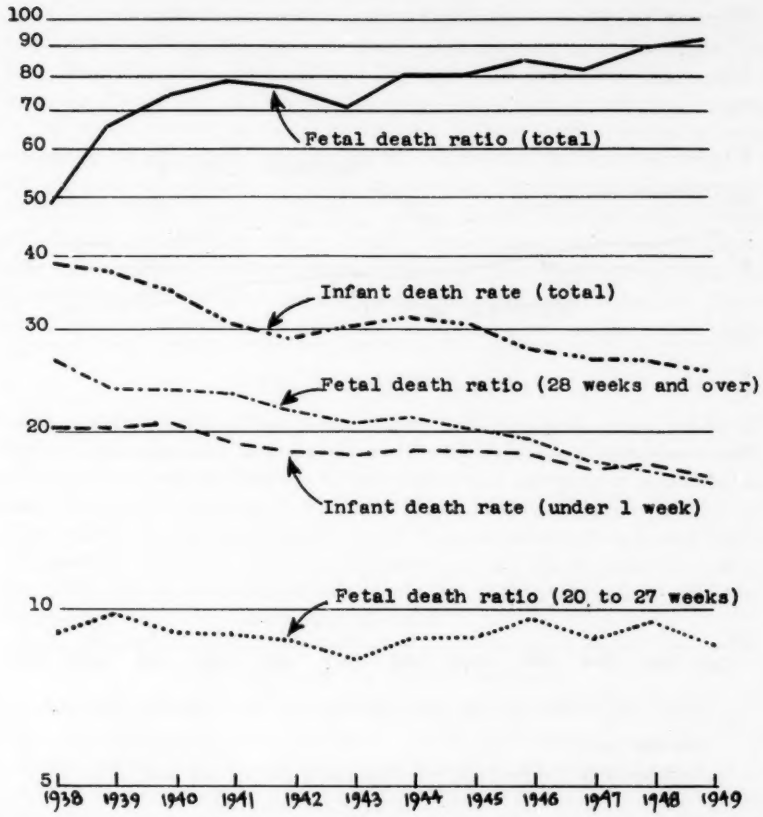

CHART 3. Fetal death ratios and infant death rates (per 1,000 live births), New York City, 1938-1949.

The similarity of the curves (representing death during fetal life and immediately after birth) is noteworthy. At the present time, an approximately equal number of fetal deaths occur at 28 weeks and over as occur among live-born infants during the first week of life. This phenomenon has not been true apparently throughout the 12 years of observation in New York City. In 1938 the fetal death ratio at 28 weeks and over was 31% greater than the death rate among infants under a week of age. The fetal death ratio for the later period of fetal life has apparently been declining faster than the early neonatal death rate, a decline of 38% for the former over the 12 years, against 17% for the latter. These two phenomena are not, of course, independent. The progress in bringing a viable fetus to term or through successful delivery prior to term has produced more liveborn infants subject to the effects of this change in state. This has seemed to have a retarding effect upon improvement in the neonatal mortality rate. Such a hypothesis presumes that those additional fetuses which are now brought to live birth constitute poorer risks, and does provide one reasonable explanation for the difficulties which are met in reducing the neonatal mortality rate. Further investigation is needed to demonstrate whether the hypothesis

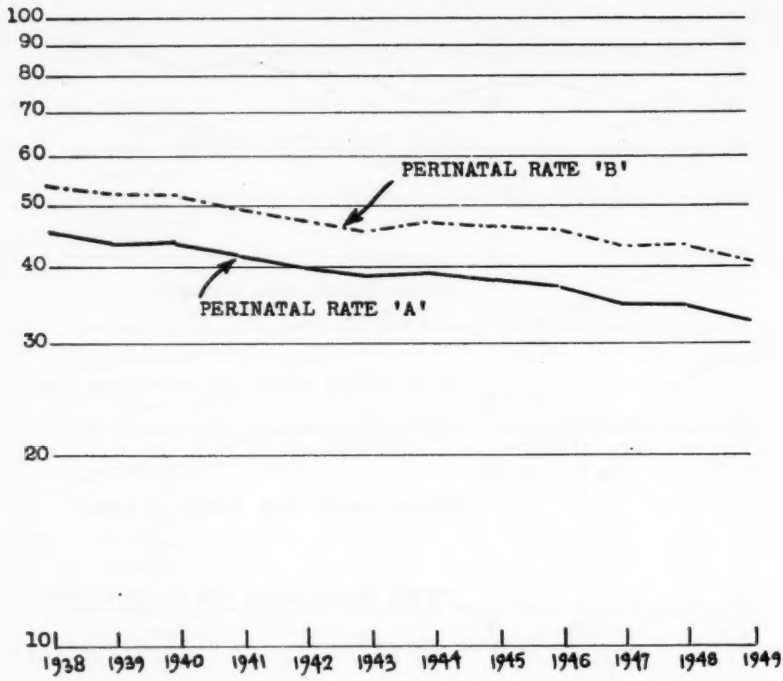

CHART 4. Perinatal rate (per 1,000 pregnancies), New York City, 1938-1949.

Perinatal rate 'A':

$$\frac{\text{Infant deaths (under 1 wk.)} + \text{Fetal deaths (28 wk. and over)}}{\text{Live births} + \text{Fetal deaths (28 wk. and over)}} \times 1{,}000$$

Perinatal rate 'B':

$$\frac{\text{Infant deaths (under 1 wk.)} + \text{Fetal deaths (20 wk. and over)}}{\text{Live births} + \text{Fetal deaths (20 wk. and over)}} \times 1{,}000$$

Note: Fetal deaths with period of gestation "not stated" are omitted.

is true, but the factor of having more "poor risk" babies in the neonatal group should be taken into consideration in any studies of changes in neonatal mortality.

It is because of this close association of the fetal and neonatal deaths that future students of the subject are being urged to measure progress by studying of so-called perinatal rates which combine the two. Such a procedure provides a more meaningful ratio than two separate ratios, a change in one of which must influence the other. When such rates are plotted, the continued downward trend demonstrates clearly that progress has been made in reducing the loss of life at the period centering around the time of birth (chart 4).

RELATION TO PREVIOUS COMPLICATIONS OF PREGNANCY

More detailed studies of the relationship of maternal complications and infant loss indicate also the high probability of certain groups of pregnant women having complica-

tions which lead to stillbirths or neonatal deaths. Bundesen's recent figures[4] from 10,000 neonatal deaths in Chicago bring this out sharply although most of the conclusions have long since been recognized. Neonatal mortality rates were highest for infants born to mothers under 20 and over 40. The rate for twins was 11 times greater than for single infants. The mothers of the premature infants who died had previous premature infants or abortions about 2½ times oftener than the mothers of the full-term infants. As gravidity increased, the neonatal mortality rate increased. The neonatal mortality rate for infants of mothers with toxemia was twice as high as for infants of mothers without toxemia. Among nonsurviving infants, breech presentations were more frequent in previable and premature infants than among those at term. Operative deliveries were accompanied by higher neonatal mortality rates than nonoperative deliveries. The rate for infants whose mothers received anesthesia was higher than for those whose mothers had not.

The Overweight Baby

Another concept is also becoming more and more clear, namely, the greater risk involved at being born too early or too late. As early as 1939 we pointed out from New York City figures the greater mortality rates of infants (white and nonwhite, male and female) weighing more than 3750 gm. at birth and later we emphasized the greater increase in the fetal death rate of heavier, more mature fetuses. Using a method of combining fetal and neonatal mortality experience we have also shown it is possible to calculate "best birth weights."[5] All such methods demonstrate clearly the much greater risk to the fetus or infant weighing more than his or her optimal weight.

Implications for Future Action

These are some of the more pertinent facts concerning infant loss with which the physician and public health official are faced. Certain others should be included to give scope to the problem. There seems to be no indication of any marked decrease in birth rates, so that we can probably expect roughly four million births a year. Although much emphasis is being put on our aging population we are actually growing younger faster than we are growing older. In the past 10 years, for example, the population over 65 increased 37% but the high birth rate increased the population under 5 by 55%. Moreover, if one considers the deaths associated with child bearing (i.e., reported fetal, maternal and neonatal deaths), one is dealing with the third leading cause of death. This is true despite the well recognized unreporting of deaths of viable fetuses. It is, perhaps, too bad that there has always been a separation of these three causes of death and that there has been so great a separation of obstetric and pediatric work. We are now at a stage when the total problem needs attack. What are the implications of these facts and what steps should be taken for action? At least five major areas of activity immediately suggest themselves.

Need for Research in Human Reproduction

The first clear implication is the need for integrated and concentrated research in this field of human reproduction. Far too little is known of the underlying causes of the mortality and morbidity in the period before and after birth. There is need to develop one or more institutes where continuing studies of these problems can be made by the embryologist, chemist, physiologist, pediatrician, obstetrician, physicist, anthropologist, sociologist, statistician—in fact by research workers of all kinds specially oriented to this

problem of the developing human young during pregnancy and early life. Certainly the great success of our many continuing ventures in studying problems related to animal husbandry and reproduction suggest that similar efforts to elucidate the factors involved in human reproduction would bear fruit.

Need for Improvement in Existing Services

The second clear implication is to recognize that many of these deaths are preventable if all mothers and infants got the care that is available in the better maternity and pediatric services and to so organize our medical and hospital world that orderly steps be taken to this end. I shall mention five areas of possible attack which can be sponsored directly by pediatricians, public health officials, and other physicians.

Because of high rate of hospitalization and the concomitant wide variation in practise in hospitals there is need to improve practise in those hospitals with poor standards. The real question is how this can be done. Will we as physicians be content to let nature take its course and hope that somehow, some day, practise will improve? Or will we in more active fashion try to speed that day along? For example, in most areas today certain basic sanitary requirements have to be met by all hospitals with newborn services. Is it too much to think such hospitals should also, for example, be asked to have blood on hand to combat hemorrhage, facilities to type blood so that the birth of an erythroblastotic infant can be foretold, to have a trained anesthetist, or adhere to the widely accepted policy of having the complicated case seen by some physician of more than ordinary skill? There is abundant evidence of need to do something about getting these practises more widely accepted. In New York City a recent study[6] indicates that in 62% of private patients delivered by breech, in roughly 40% of those delivered by midforceps or internal podalic version and, in 25% of those delivered by cesarean section, the delivery was performed without consultation with an obstetrician. Only 55 out of 76 hospitals had even provided for consultation policies on the obstetric service and in only 33 of the 55 were such policies carried out. In 45% of the hospitals blood typing was routine, with 55% requiring routine Rh determination. Fifteen of the 76 hospitals had no blood on the premises despite its ready availability in the city. In only 15 were pediatric rounds made daily on hospital newborn services. These figures are based on investigations made routinely by obstetricians and pediatricians of the Department of Health staff. An elaborate study just published by the New York Academy of Medicine[7] confirms the existence of poor standards maintained in many hospitals. In fact this study concludes: "The most striking finding is the fact that a considerable number of maternity services in this city do not meet minimum requirements for adequate care; they lack some essential facilities, are short in medical and nursing personnel, and have not formulated and implemented desirable consultation policies. A number of maternity services were found to be so wanting in necessary equipment and so faulty in their practises that they constitute a hazard to the parturient mothers and their babies." A variation in neonatal mortality rates in hospitals of from 10 per 1000 live births to above 30 was found and this with the city average at 20. Pediatric care was particularly poor in 20 hospitals. This is one example of the situation today in a large urban area—and it seems fair to assume that similar situations can be found elsewhere. These problems of improving hospital practise are ones which pediatricians can and must help solve.

Certainly improvement can be made in such a way that the freedom of medical practise is not interfered with. Yet it is not uncommon to consider any attack on this problem as interfering with the rights of physicians to practise as they wish. Even the mandatory use

of a preventative against ophthalmia neonatorum and certain quarantine measures have been carried out without basic interference with medical practise. Some health departments and medical groups are currently tackling this problem through various educational means. The cooperative venture of the American Academy of Pediatrics, the Children's Bureau, and many health officials in promulgating *Standards for Fetus and Newborn* in local communities is a step forward. But it takes more than presenting desirable standards, no matter how attractively packaged, to get them accepted. Some health departments are making available teams of consultants (pediatricians, obstetricians and nurses) to hospitals requesting service. In other areas the refresher course and the nursing institute are old favorites. All these approaches have value. It is of great importance that these activities be actively promoted and supported at the local level by the practising physicians and nurses. Basic to all is better education at the undergraduate level for physician and nurse.

Development of Additional Services

Another way of preventing some deaths has been to subsidize certain facilities and services or to pay for care for the medically indigent. Large sums are, for example, currently being spent on premature infant centers and in the care of the prematurely born. There is some question as to whether this was the most effective way to begin. It was probably the only practical way but a larger effort in preventing premature labor in those women in whom one could reasonably expect such an event might have produced not only more knowledge of the prevention of premature labor but additional saving of lives. But knowledge of the care of the premature infant was available and is more dramatic. Emphasis on the care of those prematurely born has certainly saved many lives, and has served as well to raise the quality of care for all newborns, thereby saving lives of full-term infants as well. It has probably stimulated, as well, research into the basic causes of premature labor to the end that premature birth may more effectively be prevented. Providing nutritional supplements to the pregnant woman, and obstetric consultation, or even continuing hospitalization for selected cases are devices that should be further explored and evaluated. It has not been difficult to hospitalize cases of infectious disease in certain hospitals or units of hospitals. It might also be interesting to try to hospitalize all women with premature labor in certain centers. All these methods should be more widely tried and results carefully evaluated.

Making the talents of specialists and well organized services reach a larger number of persons can also be achieved with the further development of regional schemes in which the rural and small towns receive such services from larger medical centers.

Need for Greater Cooperation of Obstetrician, Pediatrician, General Practitioner and Other Personnel

As has been repeatedly pointed out, there is great need for closer cooperation between obstetrician, pediatrician and general practitioner. In hospitals, joint staff conferences should now be a routine. Such conferences should include nurses, nutritionists, social workers and other para-medical personnel all of whom have something to contribute to the care of mother and child. Joint study of neonatal and fetal deaths similar to those made of maternal deaths by many hospitals, county medical societies and departments of health may advance knowledge and will surely highlight the problem so that more effective action of the medical and hospital community will follow.

Need for More Attention to Prenatal Care for All Expectant Mothers

Though not directly related to pediatric practise I believe that pediatricians must join, indeed help organize, efforts to bring better prenatal care to expectant mothers, particularly those mothers in whom some complications can be anticipated. A vigorous campaign to locate such women and bring better care to them will certainly bring results.

Attacking Basic Economic and Social Problems

And lastly, some day, somehow, we need to find more effective solutions to the problems created by the low economic and social status of the many families which contribute so heavily to fetal and neonatal mortality rates today. This is no simple problem, but the social cost of illness and death is fast becoming so great that these social and economic problems demand the attention of physicians as well as others.

Summary

The salient facts regarding fetal, neonatal and infant mortality in the United States are presented, using the most recent national figures available, or those from other large population groups. A plea is made for the use of perinatal mortality rates in order to obtain a better picture of the success of current programs designed to reduce infant loss.

Six areas for future attack are suggested: 1. Development of several research institutes to study the problems of human reproduction from a multidiscipline approach.

2. An organized program to raise standards of care in all lying-in hospitals with particular emphasis on activities which can be carried on by nurses and doctors at the local level.

3. Further experimentation with and development of ways to supply better service or pay for medical care for certain groups. More attention could be paid to regional plans whereby services of large medical centers are brought to smaller, less well cared for areas; to hospitalizing women with previous history of or current complications of pregnancy, including labor; to providing expert pediatric and obstetric consultation more freely, to supplementing the prenatal diet, et cetera.

4. Acceleration of activities which bring about closer cooperation between obstetric and pediatric services with full cooperation of general practitioners, nurses, nutritionists and all those involved in the care of mother and baby. More local studies of neonatal deaths with the studies used as the basis for community action and professional education.

5. Development of better prenatal service for all mothers in the local community.

6. Continued experimentation with methods of solving the many social problems created by the low economic and social status of those families which contribute so heavily to fetal and neonatal mortality rates today.

Acknowledgment

Credit is due Mr. Carl Erhardt and his staff for their statistical assistance.

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SPANISH ABSTRACT

Aspectos de Salud Pública en los Problemas de Interés General de la Pediatría Neonatal

La autora hace una revisión de los hechos más salientes en relación con la mortalidad infantil y fetal usando las cifras nacionales más recientes y los sumariza en las siguientes afirmaciones:

1. La mortalidad infantil ha sido reducida en dos terceras partes desde 1915. La caída más grande —más del 80%—fué entre aquellos lactantes que sobrevivieron al primer mes de la vida. La siguiente caída es de 52% y se registró en el coeficiente de mortalidad neonatal y la menos marcada de 31% que corresponde a la mortalidad del primer día.

2. Los coeficientes de mortalidad infantil y neonatal descendieron mas rápidamente desde 1935 que en los años anteriores.

3. Existen amplias variaciones en los coeficientes de las áreas urbanas y rurales y en los distintos grupos económicos. "Las probabilidades de sobre vida de un niño dependen en gran parte del sitio donde vive de las circunstancias de sus padres."

La presencia de tantos niños de la nación en las familias con entradas bajas (43% en familias con entradas de menos de $60 dólares a la semana) y la tendencia de las familias con más niños a tener entradas económicas más bajas, complica el problema de asegurar mejor atención médica a madres y niños.

La concentración de los médicos en las áreas urbanas crea otros problemas a la reducción futura de los coeficientes de mortalidad.

4. Los coeficientes de mortalidad de niños blancos y no blancos están decreciendo aproximadamente el mismo porciento pero ha cambiado poco el riesgo mayor que tiene un niño negro, aún en 1949 fué de 47.3 por cada 1000 nacimientos vivos registrados en los niños negros y 28.9 en los blancos.

5. Persiste la bien conocida diferencia entre los coeficientes neonatales de ambos sexos con coeficientes relativamente más altos para los hombres.

Se sugieren seis áreas para el ataque futuro de estos problemas:

1. Formación de varios institutos de investigación para estudiar los problemas de la reproducción humana desde múltiples disciplinas de acercamiento.

2. Un programa organizado para mejorar los standards de atención en todas las maternidades enfatizando particularmente aquellas actividades que pueden ser realizadas por enfermeras y doctores en el media local.

3. Futura experimentación y desarrollo de procedimientos para proveer mejor servicio o el pago de la atención médica de ciertos grupos. Debe prestarse más atención a los planes regionales haciendo que los servicios de los grandes centros médicos sean llevado a las zonas pequeñas, cuya atención médica es inferior: hospitalización de mujeres con las complicaciones comunes del embarazo y parto ó con antecedentes de dicha naturaleza, suministro de consulta obstétrica y pediátrica con más liberalidad, suplementar la dieta prenatal, etc.

4. Acelerar las actividades que resulten en una cooperación más íntima entre los servicios obstétricos y pediátricos con colaboración completa de los médicos generales, enfermeras, nutriólogos y de todos aquellos elementos involucrados en la atención de madre y niño. Más estudios locales de las muertes neonatales usados como base para programas de acción de la comunidad y de educación profesional.

5. Desarrollo de un mejor servicio prenatal para todas las madres de la comunidad local.

6. Experimentación continua de métodos para resolver los muchos problemas sociales creados por las bajas condiciones económicas y sociales de aquellas familias que contribuyen tan grandemente en los coeficientes actuales de mortalidad fetal y neonatal.

CLINICAL DIAGNOSIS OF GENERALIZED CYTOMEGALIC INCLUSION DISEASE

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GENERALIZED cytomegalic inclusion disease was recognized as early as 1904.[1,2] It has been described under a variety of names, including "generalized salivary gland virus infection," "inclusion disease," "protozoan cell disease" and others. The present investigators believe that the term "generalized cytomegalic inclusion disease," as proposed by Wyatt et al.,[3] is most descriptive of the condition.

Most reports have been concerned with the description of characteristic large cells containing intranuclear inclusions which occur as "incidental" findings in the salivary glands of infants in from 10 to 32% of routine autopsies.[4-6] However, inclusion bodies which appear to be identical with those described in the salivary glands have been found in other organs in from 1 to 2% of routine autopsy reports on infants.[4,5] A study of those patients reported to have the generalized form of the disease, particularly the detailed reports of Wyatt et al.,[3] Smith and Vellios[7] and Worth and Howard,[8] leads to the conclusion that this is a specific disease entity which is usually fatal in infants under two months of age. The assumption is also made in the foregoing reports that this disease is probably the result of a specific viral infection and that infection occurs in utero.

The purpose of the present report is to describe the first patient in whom the diagnosis of generalized cytomegalic inclusion disease was established clinically.

REPORT OF A CASE

Patient was first seen at 17 days of age. Referring physician reported that he had jaundice, petechiae, thrombopenia and hepatosplenomegaly at birth. He was the product of a full-term pregnancy. However, birth weight was only 1758 gm. Pregnancy appeared to be normal except for one episode of minimal vaginal bleeding. Blood examination done on day of birth was as follows: RBC count 5.4 million/cmm.; WBC count 35.6 thousand/cmm.; Hgb. 17 gm./100 cc.; polymorphonuclear leukocytes 22%; lymphocytes 74% and 81 normoblasts/100 WBC. Platelets were not seen.

Prior to admission patient had received 2 blood transfusions because of progressive anemia. Referring physician reported that spleen, which had been at iliac crest at birth, had gradually decreased in size and that the patient had been passing clay-colored, blood-tinged stools.

Physical Examination: At admission weight was 1725 gm. (Fig. 1). He had a good cry and appeared more active and vigorous than his weight would indicate. Temperature was 37.8 C., PR 144/min. and respiration 84/min. Skin was deeply jaundiced. Multiple petechiae were present over entire body. Head was small, measuring 26 cm. in circumference. Anterior fontanel was open but not bulging. Sclerae were deeply icteric. Extraocular movements and pupillary reflexes were normal. Fundi were normal. Ears, nose and throat were normal. Chest was symmetric and measured 26.5 cm. in circumference. Abnormalities of heart or lungs could not be detected. Abdomen was distended, with tense, shiny skin and prominent superficial veins. Both liver and spleen were palpated

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FIG. 1. Patient on admission. Note distended abdomen, prominent veins, emaciation and multiple petechiae.

FIG. 2. Skull RG demonstrating multiple areas of intracranial calcification.

FIG. 3. RG demonstrating sclerosis of long bones with diminished density at ends of shafts.

about 5 cm. below costal margins. There was generalized, shotty lymph node enlargement. Rest of physical examination was negative.

Laboratory Data: Initial laboratory findings were as follows:

Blood: RBC count 1.6 million/cmm.; Hgb. 8.1 gm./100 cc.; WBC count 9.0 thousand/cmm.; differential polymorphonuclear leukocytes 33% with 21% of these unsegmented cells, lymphocytes 54%, monocytes 3%, eosinophiles 3%, basophiles 3%. Many target cells were seen and there was moderate anisocytosis, poikilocytosis and polychromatophilia. The platelet count was 17,820/m^3.

Blood type A, Rh-positive, Coomb's test negative. Fragility test.—Control: Initial hemolysis .42, complete .34; Patient: Initial hemolysis .46, complete .36.

Urine: Deep yellow in color, pH 5.5; Sp. Gr. 1.025. Albumin, sugar, acetone and urobilinogen negative. Foam test positive. Urinary sediment contained numerous granular casts and large numbers of epithelial cells. No red or white blood cells were seen.

Blood Chemistry:

Serum proteins	6.16 gm./100 cc.
Albumin	4.23 gm./100 cc.
Globulin	1.95 gm./100 cc.
A/G ratio	2.19 gm./100 cc.
Van den Bergh's direct	+++
Bilirubin	6.4 mg./100 cc.
Icterus index	90
Phosphorus	3.82 mg./100 cc.
Phosphatase	5.73 Bodansky u.
Thymol turbidity	1.0 u.
Cephalin flocculation	24 hr. — 0
	48 hr. — +

Miscellaneous: Blood serology was negative on both mother and child. Mother's blood was also type A, Rh-positive. Repeated blood cultures were negative. Several attempts to aspirate bone marrow were unsuccessful. It was found that cortex of femur, tibia, and iliac crest were unusually hard and difficult to penetrate. Only a small amount of diluted marrow could be obtained and nothing was gained from a study of these specimens.

Skull RG were taken which demonstrated multiple areas of intracranial calcification (Fig. 2). Ventriculograms confirmed impression that these areas of calcification were primarily in relation to ventricular walls. Roentgenogram of long bones showed unusual sclerosis of shafts with evident areas of diminished density at ends of long bones (Fig. 3). Films of chest and abdomen were noncontributory.

Differential Diagnosis.—Initial clinical impression was that this patient had erythroblastosis. This diagnosis, however, was promptly excluded when it was found that both baby and mother were blood type A, Rh-positive, and the former had a negative Coomb's test. Syphilis was ruled out by negative serology on the mother and child. Sepsis was eliminated by repeated negative blood cultures. Dual diagnoses of toxoplasmosis and inclusion body disease were then considered. Blood was drawn from both mother and child for Toxoplasma-neutralizing antibody testing. Test performed was micro-dye method of Sabin and Feldman.[9] Patient's serum gave a positive reaction to dilution 1:64 and mother's serum tested positive 1:128. Patient's blood was also cultured intraperitoneally in mice but no Toxoplasma were found in peritoneal fluid of animals after 9 days, nor were any organisms detected after serial transfer of peritoneal fluid to other mice. Ventricular fluid, obtained in fourth week of life, was injected intraperitoneally in young mice, but failed to yield any growth of Toxoplasma in 9 days. Ventricular fluid was noted to be xanthrochromic with protein content 101 mg./100 cc.

In an attempt to establish the diagnosis of generalized cytomegalic inclusion disease multiple specimens of fresh urine were centrifuged and sediment was examined by various technics. Sediment was consistently characterized by large numbers of granular casts and epithelial cells. These cells were present singly and in sheets and clumps, and appeared to have originated from desquamated tubular epithelium (Fig. 4). They were found to stain best if urine were rendered slightly alkaline and Jenner-Giemsa's or MacNeal's tetrachrome stains were used. Satisfactory specimens were also obtained with Papanicolaou technic. Cells completely characteristic of those described in the kidneys of patients with inclusion body disease were not seen.[10] Several large objects were seen, however,

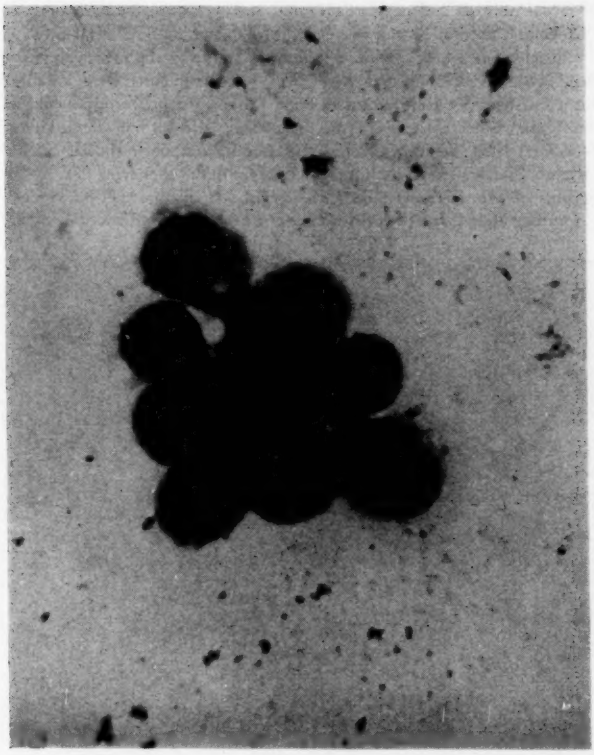

FIG. 4. Clump of epithelial cells from urine with cytoplasmic inclusions.

which were thought to represent necrotic giant cells (Fig. 5). A large number of intact epithelial cells contained basophilic inclusions in their cytoplasm. Similar inclusions were not observed in urine of 10 other male infants 1 mo. of age or younger, with various diagnoses including chronic renal disease. On the basis of clinical findings plus urine findings, particularly the unmistakable evidence of tubular epithelial desquamation, the diagnosis of generalized cytomegalic inclusion disease was made.

Hospital Course.—Patient's condition in hospital gradually but progressively declined. A dry hacking cough developed and there were frequent episodes of respiratory difficulty associated with feedings. Fine rales could be heard over both lung fields on several occasions. Due to respiratory complications it became necessary to feed by gavage. Showers of petechiae continued to appear. Transfusions had but a transitory effect on the anemia, and treatment with vitamin K, crystacillin, sulfadiazine, chloromycetin®, and parenteral fluids was ineffective. Patient died 5 wk. after admission.

Autopsy.—Body weighed 2300 gm. Definite icterus of skin and of sclerae. Petechiae were numerous in skin of entire body. Head measured 29 cm. in diameter. Posterior fontanel was closed; anterior measured 1 by 1 cm.

Liver and spleen were enlarged and firm, weighing 220 and 60 gm., respectively. A small amount of clear yellow fluid was present in peritoneal cavity. Kidneys showed bile staining and petechiae of cortices. Irregular dark red firm noncrepitant foci were present in lungs, more prominent in upper lobes. Salivary glands were not examined.

Brain was small and firm, weighing 180 gm. (average brain weight for size, 330 gm.) There

was a region of recent necrosis and hemorrhage in L premotor area, measuring 3.5 cm. in diameter. There was an irregular thin walled cyst, 1.5 cm. in diameter in R parietal area. It did not communicate with ventricle. Surface of brain in region of cyst was slightly depressed and firm, with irregular narrowed gyri. Surfaces of gyri were finely wrinkled. Sulci were broad. Brain was firm and of a rubbery consistency. A band of calcification was present in cortex, 2 mm. beneath surface. This was especially noticeable in region of the cyst. Many pale yellow calcified foci were scattered throughout the cerebral tissue in this region. Basal ganglia contained similar calcified foci. Lateral ventricles were slightly dilated. There was focal calcification in the ependyma.

Posterior segments of eyes were examined. An irregular light brownish-yellow focus of discoloration measuring approximately 2 by 1 mm. was present in region of R macula. A similar focus was

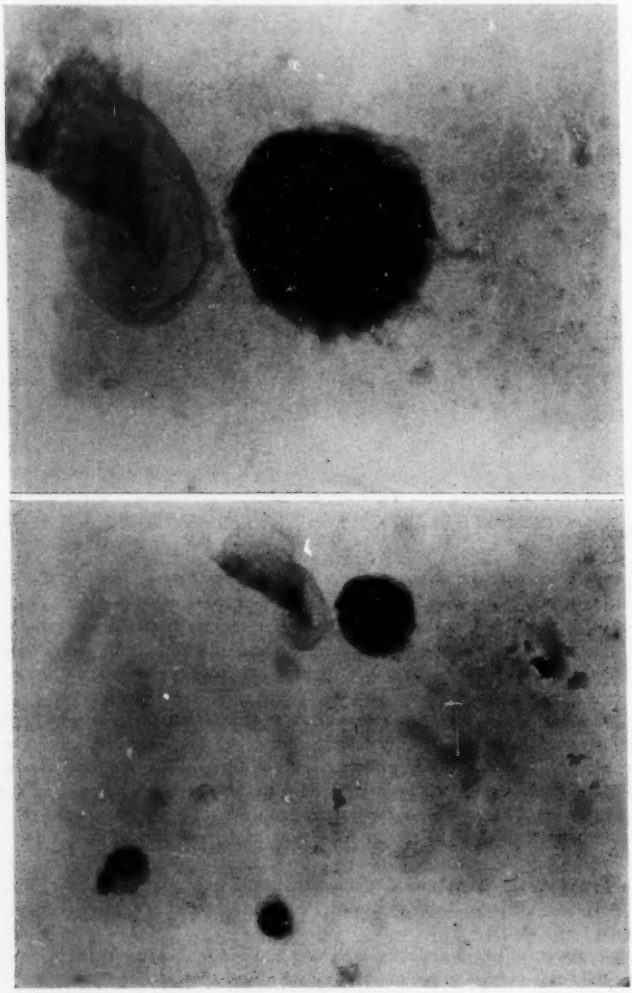

FIG. 5A. Necrotic giant cells from urine sediment (× 1500). Low power views (× 500) demonstrate size in relation to epithelial cells. See Fig. 5B on opposite page.

present in retina opposite the macula across the nerve head. In the medial portion of L retina, approximately 3 disc diameters from the nerve head, there were a cluster of yellowish-grey foci, entire cluster measuring 2 mm. in diameter. Retina elsewhere was not unusual.

Intranuclear and cytoplasmic inclusions typical of salivary gland viral disease were identified microscopically in epithelial cells of renal tubules, acini and ducts of pancreas, acini of thyroid, pars distalis of hypophysis, and lying free in alveoli of lung. Intranuclear inclusions were large basophilic round opaque bodies with a peripheral clear halo. Clumped basophilic material was present on well-outlined nuclear membrane. Cytoplasm of the cells containing the inclusions was increased and filled with minute inclusions which were slightly basophilic. Both intranuclear and cytoplasmic inclusions were Feulgen-positive. Both gave a positive reaction when stained with periodic acid Schiff reagent.

Inclusions were not observed in liver. There was staining of parenchymal cells and Kupffer's

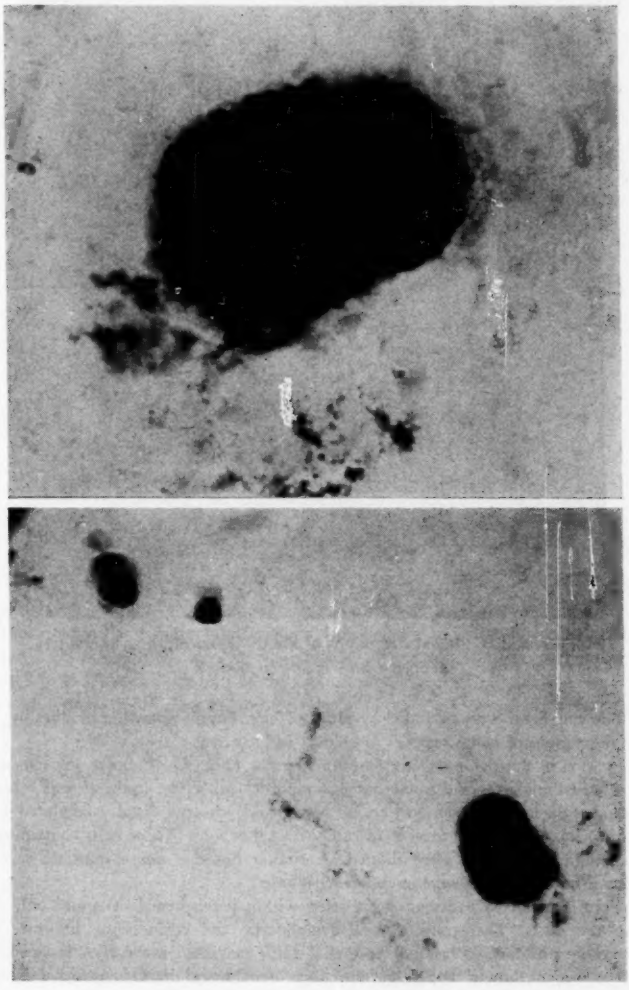

FIG. 5B. For legend, see Fig. 5A, opposite page.

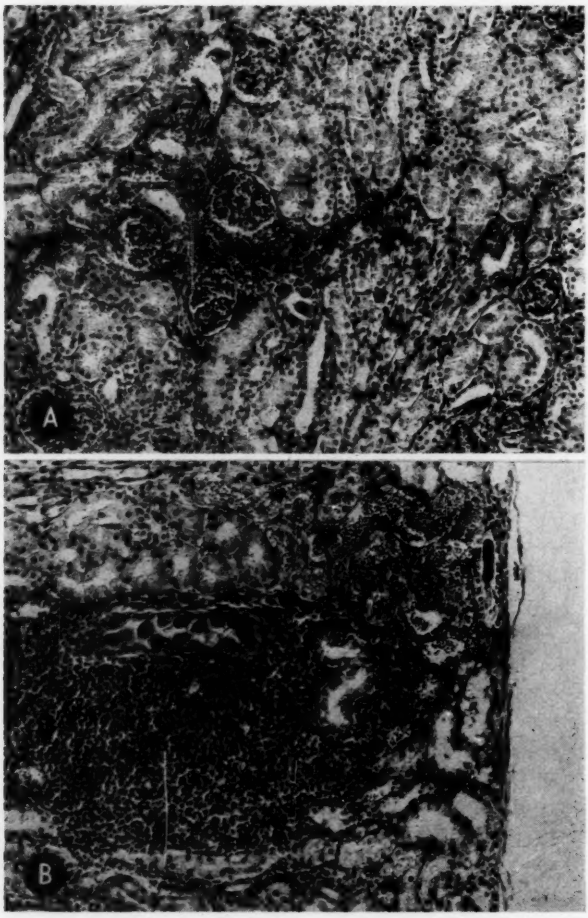

FIG. 6 A and B. Photomicrographs of kidney demonstrating interstitial nephritis and inclusion bodies.

cells by bile. Bile canaliculi were occluded by plugs of bile. Focal infiltration of liver by cells similar to that seen in the regions of inclusions was in kidneys and pancreas.

There was severe interstitial nephritis of both kidneys (Fig. 6). Cellular infiltrate consisted of mononuclear cells, lymphocytes and numerous eosinophilic leukocytes. Infiltrate was especially dense surrounding glomeruli in the outer portion of cortex and adjacent distal convoluted tubules containing inclusions. Inclusions were present in cells of renal tubules. Those cells containing inclusions were enlarged and tubules were often dilated. A similar but less dense infiltrate was present in peripelvic region. Pigmented casts were in collecting tubules.

Inclusions were frequent in pancreas, most often within parenchymal cells and only occasionally in cells lining the ducts. There was a focal lymphocytic and eosinophilic infiltrate present. In thyroid and anterior pituitary, occasional epithelial cells contained inclusions. Inclusions were not present in spleen which showed hyperemia and foci of extramedullary hematopoiesis. A rare cell containing intranuclear inclusions was found free within alveoli of the lungs. There was a significant

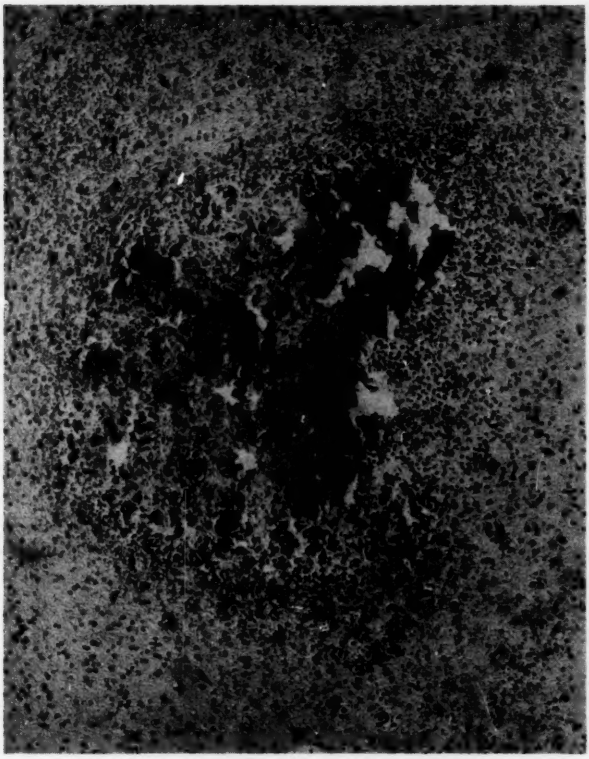

FIG. 7. Focus of necrosis and calcification in brain.

interstitial pneumonia with thickening of the alveolar septae and infiltration by lymphocytes, plasma cells, eosinophilic and occasional neutrophilic polymorphonuclear leukocytes.

A recent hemorrhagic infarct of L premotor region was observed. An organizing meningitis and pachymeningitis were present over cerebral hemispheres and spinal cord. There was a diffuse perivascular encephalomyelitis with an infiltration of lymphocytes and slightly larger mononuclear cells. Band-like areas of calcification were in midportion of cortex in many portions of brain, most noticeable in R parietal area in region of the cyst. Scattered foci of calcification were present in the deeper cerebral tissues, basal ganglia and ependyma (Fig. 7). Organisms of toxoplasmosis could not be identified.

Foci of lymphocytic and histiocytic infiltration with glial proliferation were in the ganglion layer of retina. Blood vessels were dilated in these foci. Ganglion cells were not identifiable. In foci of cellular infiltration the region of the ganglion layer was severely thickened. Adjacent portions of retina showed some loss of ganglion cells with occasional lymphocytes and histiocytes present. There was slight glial proliferation without focal thickening.

DISCUSSION

The literature on cytomegalic inclusion disease has been recently surveyed by Wyatt et al.[3] and Smith and Vellios.[7] Several points seem worthy of mention:

1. Intranuclear inclusions similar in morphology to those seen in generalized cytomegalic inclusion disease of infancy have been frequently described in the salivary glands

of various laboratory animals.[11-15] These have been demonstrated to represent specific reactions to species specific viruses.[16-24] Pappenheimer and Slanetz[25] have described a generalized visceral disease of guinea pigs associated with intranuclear inclusions and have suggested the possibility of a virulent form of the usually innocuous salivary gland virus.

2. Intranuclear inclusions in cerebral lesions associated with encephalitis have been described.[26-29]

3. Intranuclear inclusions have been produced experimentally by the injections of various substances such as lead, aluminum and ferric compounds, bismuth and salyrgan theophylline (salyrgan®).[30-33] In general these are not morphologically identical to the inclusions of generalized cytomegalic inclusion disease.

4. The described cases of inclusion disease fall into four groups: (a) those found in the salivary glands as an incidental observation in routine autopsies.[4,5] (b) Those detected in association with debilitating disease.[34-39] These are particularly exemplified by cases reported in adults and suggest the possibility that a latent viral infection may be stimulated by loss of resistance. (c) Those found in association with pertussis[40-43] and with viral pneumonia.[44,45] Inclusions described in the latter disease are not morphologically identical with those described in generalized cytomegalic inclusion disease. (d) Those found in newborn infants where death has occurred in the absence of other disease. It is with this latter group that we are most concerned.

Smith and Vellios[7] have abstracted the 69 cases of inclusion disease in infants and children reported in the literature and add 20 cases from their laboratory. Thirty-seven of the total 89 cases occurred in newborn infants or in infants dying under two months of age. Valid conclusions cannot be drawn from a survey of this group, since the majority are reported without sufficient clinical detail.

There is, however, a striking similarity in the clinical observations on infants dying in the neonatal period with this disease. This similarity is illustrated by Smith and Vellios[7] (Cases 1, 2 and 3), Wyatt et al.[3] (Cases 4, 5 and 6), Andrews and Miller [46] (Case 2), Kinney[29] (Case 2), Cappell and McFarlane[10] (Case 1) and the single cases described by Wanstrom,[47] Worth and Howard[8] and Goodpasture and Talbot.[48]

A general clinical syndrome can be drawn from the above cases and from the patient described in the present report. Such a patient is apt to be a premature or immature infant with symptoms beginning at birth. Jaundice is usually present at that time or develops soon in the neonatal period. Showers of petechiae are seen with accompanying thrombopenia and hemorrhagic manifestations. Such hemorrhages are most frequently from the stump of the umbilical cord but may be manifested by hematuria, melena or hematemesis. Hepatomegaly and splenomegaly are pronounced. There may be an anemia resulting from hemorrhage. Numerous erythroblasts may be found in the peripheral blood. Examination of the skull roentgenogram may demonstrate small intracranial calcifications similar to those seen in toxoplasmosis. The urine may demonstrate large numbers of epithelial cells among which intracytoplasmic inclusions and perhaps cells with specific intranuclear inclusions may be identified.

The differential diagnosis is made from syphilis, erythroblastosis fetalis, toxoplasmosis and inclusion disease. The first is easily eliminated by blood serology although the possibility of syphilis as an etiologic factor has been entertained by several authors.[1,2,49-52] Erythroblastosis may be excluded by appropriate blood grouping and the Coomb's test.

Toxoplasmosis has not previously been considered in the differential diagnosis of generalized cytomegalic inclusion disease although several authors have considered the intranuclear inclusion to be a protozoan parasite.[1, 2, 50, 53–55] Goodpasture and Talbot[48] were the first to point out that the peculiar cells in this disease were not protozoan parasites but were probably derived from normal cells. Muller[56] and Wagner[57] pointed out that it would be unlikely for protozoan parasites to cross the placental barrier.

Generalized toxoplasmosis was a reasonable diagnosis on the patient herein reported until it was eliminated by the low titers of antibody response[58] and by the failure to demonstrate the organism by animal inoculation or by histologic methods; neither was the pathologic histology of the brain lesion characteristic of toxoplasmosis.[59] It should be noted that brain lesions are not uncommon in the reported cases of generalized cytomegalic inclusion disease, and other cases[3, 47] have been reported to demonstrate small areas of intracerebral calcification similar to that seen in toxoplasmosis. Worth and Howard[8] described a few cells resembling the pseudocysts of toxoplasmosis and Wyatt et al.[3] indicated that the epidemiologic problem was similar to that of toxoplasmosis. In none of the previously reported cases, however, has the possibility of toxoplasmosis been completely eliminated as an etiologic factor.

With the above possibilities excluded, the diagnosis of generalized cytomegalic inclusion disease remains. Wyatt et al.[3] were the first to suggest that examination of the urine might yield a clue to the diagnosis of this disease and it was as a result of their suggestion that the urine was carefully studied in the present case. There can be little doubt that the urine sediment in this disease reveals an unusual degree of exfoliation of epithelial cells. These cells presumably arise from the upper urinary tract. After prolonged study the present authors are convinced that the intracytoplasmic bodies are abnormal and that they do not represent artefact resulting from superimposed urate or phosphate crystals. The authors are not completely convinced that they represent inclusion bodies; neither are they entirely satisfied that the large necrotic cells pictured represent the large cells with intranuclear inclusions seen in tissue section, since no characteristic cells of this type could be found in the urine sediment. However, it is suggested that, in the presence of the characteristic clinical syndrome described, with the other diagnostic possibilities excluded by appropriate tests and supported by the finding of abnormal urine, the clinical diagnosis of generalized cytomegalic inclusion disease can be established.

Summary and Conclusions

A case of generalized cytomegalic inclusion disease is described in which, for the first time, the diagnosis was established during the life of the patient. The clinical syndrome is delineated and the differential diagnosis discussed. It is suggested that the diagnosis of the syndrome can be made clinically in the neonatal period by study of the urine sediment.

Acknowledgment

The authors wish to thank Dr. J. K. Frenkel of Rocky Mountain Laboratories for his courtesy in examining the tissue sections in the case reported.

Addendum

Since this paper was submitted for publication, Dr. George Fetterman of the University of Pittsburgh has presented an exhibit at the 1952 Annual Meeting of the American

Academy of Pediatrics at Chicago, demonstrating the clinical diagnosis of the disease by examination of the urine sediment (Am. J. Clin. Path. **22**:424, 1952). The present work will serve to corroborate the findings of Dr. Fetterman.

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SPANISH ABSTRACT

El Diagnóstico Clínico de la Enfermedad por Inclusión Citomegálica Generalizada

Esta enfermedad ha sido descrita bajo distintos nombres, como infección viral generalizada de las glándulas salivales, enfermedad por inclusión, etc. y fué reconocida desde 1904. La mayor parte de los reportes se ocupan de describir los hallazgos incidentales de grandes células características conteniendo inclusiones intranucleares en las glándulas salivales de lactantes en autopsias de rutina, pero se han reportado en otros órganos.

Los estudios de los enfermos con la forma generalizada de la enfermedad llevan a la conclusión de que es un padecimiento específico generalmente fatal en niños de menos de 2 meses de edad, suponiéndose que sea el resultado de una infección viral específica y que la infección ocurre en el útero.

Los autores reportan el primer caso de este padecimiento en el cual se hizo el diagnóstico por la clínica y los datos urinarios, particularmente los datos inequívocos de descamación del epitelio tubular comprobándose por la autopsia. Con la historia clínica de su enfermo y de otros casos de la literatura delinean un síndrome clínico que lo condensan en la forma siguiente: es factible que el enfermo sea un prematuro o lactante inmaduro con síntomas desde el nacimiento como ictericia que generalmente está presente al nacer el niño o la hace pronto en el período neonatal. Hay numerosas petequias acompañadas de trombopenia y manifestaciones hemorrágicas, frecuentemente del muñón del cordón umbilical pero pueden manifestarse también bajo la forma de hematuria, melena o hematemesis. La hepato y esplenomegalia son pronunciadas. Puede haber anemia a consecuencia de las hemorragias. En la sangre periférica pueden encontrarse numerosos eritroblastos. El estudio roentgenológico del cráneo puede demostrar pequeñas calcificaciones intracraneanas similares a las que se ven en la toxoplasmosis. La orina, como sucedió en el caso de los autores, puede presentar numerosas células epitelias en las que se pueden identificar inclusiones intracitoplasmáticas y quizás células con inclusiones intranucleares específicas.

El diagnóstico diferencial en tal síndrome clínico incluye el de la sífilis, eritroblastosis fetalis, toxoplasmosis y la enfermedad por inclusión citomegálica generalizada. La sífilis puede eliminarse por la serología específica, la eritroblastosis por la determinación de grupos y la prueba de Coomb, la eliminación de la toxoplasmosis es necesaria pues se ha pensado que las inclusiones intranucleares podrían ser protozoarios; es posible hacerlo por los títulos de anticuerpos, e inoculaciones en animales. Excluídas estas posibilidades queda por ratificar el diagnóstico de enfermedad por inclusión citomegálica generalizada y como fué sugerido por Wyatt y comprobado en este enfermo el sedimento urinario revela un grado desusual de exfoliación de células epiteliales que presumiblemente provienen del aparato urinario superior.

Los autores están convencidos, después de un estudio concienzudo, de que los cuerpos intracitoplasmáticos son anormales y que no son atefactos; no están completamente seguros que representen cuerpos de inclusión, ni tampoco que las grandes células necróticas que encontraron en el sedimento urinario de su enfermo sean las células grandes con inclusiones intranucleares que se vieron en las secciones de tejido, ya que no pudieron encontrar células características de este tipo en la orina. Sin embargo, sugieren que en presencia del síndrome clínico característico descrito y eliminadas las otras posibilidades diagnósticas por medio de las pruebas de laboratorio apropiadas y respaldado por los datos urinarios anormales, puede hacerse el diagnóstico clínico de enfermedad por inclusión citomegálica generalizada.

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Round Table Discussion

USE OF ACTH, CORTISONE AND ALLIED SUBSTANCES

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Chairman Dorfman: We thought that this subject was so broad and had so many ramifications that an attempt at complete coverage would result in nothing but a listing of the diseases in which ACTH and cortisone have been used. Therefore, it would seem instead worth while to consider general problems relating to ACTH and cortisone and then proceed to a discussion of a limited number of diseases. It is going to be difficult for us to give an expert opinion on every possible phase of this subject.

We should consider first of all: (1) What type of therapy these drugs represent and (2) how the effects observed relate to the pathogenesis of the diseases in question. When the announcement of the effect of ACTH and cortisone was made in 1949, they were heralded widely by many people as a new approach to the disease state and consequently these agents were studied in a wide variety of apparently unrelated diseases. Originally there was great enthusiasm. I can recall attending the first Armour conference; it was more like attending a meeting of a mystic cult than a scientific meeting. Everybody arose and shouted, "I, too, have seen the miracle!"

Since that time investigators have come to a more careful assessment of the usefulness of these drugs. We now are in the process of a swing toward a more pessimistic viewpoint, with some people saying, "they are not any good for anything, they are just poison and shouldn't be used at all." Most people who have thought about the problem feel that the truth lies somewhere between the extremes. ACTH and cortisone are not effective in all diseases. They have some usefulness and we hope to explore this usefulness this afternoon.

One of the major questions is the theoretical problem of whether the course of certain diseases is influenced by hormone therapy. Let us not consider for the moment whether these changes are beneficial. The very fact that changes occur in a sick person with the administration of the adrenal hormone is of great importance. Does this mean that the disease itself is related to the adrenal cortex? The first response of many to the knowledge of the action of these drugs was that we now had found a common mechanism of all diseases. There was widespread opinion that the existence of disease states was based upon the disturbance of the delicate regulation by the adrenal gland. At the present time many people doubt this view and are beginning to look at the action

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of these hormones in a somewhat different manner. To me, the present evidence does not indicate that the wide range of diseases which are influenced, leaving out for the moment, Addison's disease, is based on adrenal insufficiency. I would propose rather that if a hyperadrenal state is induced, the organism no longer responds in the normal manner. That, I think, everybody will accept as true. The abnormal response is not restricted to the usually measured metabolic effects, but extends also to the ability of the organism to respond in a manner which produces the symptoms of many diseases. Thus, the hyperadrenal organism does not respond with inflammation in the normal way, does not respond hematologically in the normal way, does not respond with hyperthermia and pain and many other manifestations. These changes do not necessarily have any direct relationship to the fundamental etiology of any other particular syndrome. Whether the inhibition of these manifestations of disease is beneficial or harmful to the organism will vary with circumstances. This idea we will explore later. One reason this new view has been questioned is the fact that in some circumstances therapeutic effects are obtained without any evidence of hyperadrenalism. The most striking of such situations is local therapy, such as in the eye, and possibly Dr. Potts can say whether he thinks this is evidence against the idea of a hyperadrenal state.

Dr. Potts: When considering therapy of diseases of the eye with the cortical and cortical-like hormones, one is dealing with a particularly unique situation for a number of reasons. The first of these reasons is that the eye, unlike almost any other organ in the body, is an example of micro-engineering. Everything is on an extremely minute scale. The acute vision of the eye resides in a volume which is bounded by a layer 0.1 mm. thick and 1 mm. in diameter. That is the macula lutea, and if this macular area is destroyed, the patient no longer has vision better than 20/200. He can see only the big E at the top of the chart, and for industrial purposes he is blind. So that a disease that only affects this small area can cause tremendous damage all out of proportion to the effects of such a lesion elsewhere in the body. Consider, again, the passage which the aqueous humor has to take from the posterior chamber to the anterior chamber through a little slit between iris and lens, some 3 mm. in diameter perhaps 0.5 mm. in thickness. If this small channel is completely blocked by fibrous exudate, there is no exit for the aqueous humor and secondary glaucoma and loss of the eye results.

Consider the outflow channel for the aqueous humor through Schlemm's canal; again a minute 0.1 mm. opening, an annulus some 12 mm. in diameter. When one considers that such minute damage can ruin the eye for all practical uses, one realizes that with eye diseases we are dealing with diseases of the smaller order of magnitude than one deals with elsewhere in the body.

An abscess elsewhere in the body is a relatively minor matter and rarely has an unfavorable outcome. But such infections in the eye usually mean complete loss of the organ and one does not even consider them from a point of view of therapy because at the time of detection this situation is hopeless. Thus, the eye diseases that we are talking about are relatively mild diseases and are conceivably amenable to therapy by relatively mild agents. In regard to these diseases, by some stroke of fortune, those which are amenable to treatment are almost all characterized by long remission. Many are self-limiting and do not reactivate, so that if one can prevent this microdamage during the acute phase of the disease, spontaneous remission will take care of the patient for indefinitely long periods of time. The cases of chorioretinitis are worth thinking about in this connection.

The fact is that many eye diseases, particularly of the anterior segment of the eye, are amenable to local therapy with cortisone or cortisone acetate. Application of a relatively dilute suspension of cortisone, very little of which gets into the eye at all, is enough to be adequate therapy for severe diseases of the cornea. What tiny amount of the material actually does get into the eye and what the chemical form is when it actually penetrates is still a matter of speculation. Our own efforts at the Western Reserve University Laboratory have run up against a stone wall because of inadequate analytic methods and probably until isotopically labelled cortisone is available generally, that question will have to remain unanswered. The fortunate circumstances mentioned above make eye diseases unique, even when they have to be treated by systemic therapy.

There is one additional point in regard to this question of whether normally reacting tissues are or are not advantageous. That again is very specific in the case of eye diseases. The cornea is a highly specialized organ in that its function depends on complete transparency. Among the normal reactions of tissue to injury is the new formation of blood vessels. In the case of many eye diseases the cornea becomes atavistic and begins to grow blood vessels which penetrate from the limbus. If this activity can be put in abeyance by some drug such as cortisone until the danger is past, until

the vessel-stimulating substance disappears from the local area, then a great benefit results to the patient.

Chairman Dorfman: You think, then, that in the case of treating eye diseases a hyperadrenal state in a cellular sense is produced in a localized area of the body, and therefore no other effects of the adrenal hormones are observed.

Dr. Potts: That is right.

Dr. Robert Warner, Buffalo, N.Y.: There are 2 observations that may stand in the way of this interpretation: the first is experimental and the other refers to the behavior of allergies. First is the experiment done with wild rats which showed that you can't shock them like you can the laboratory rats. The laboratory rat has lost its sense of the alarm reaction, not having to live by its wits. These rats don't actually have a deficiency, but a deficiency of response to normal stimuli. In line with this interpretation is the situation of patients having allergic manifestations such as asthma or skin diseases who develop pneumonia or mastoiditis. When the alarm reaction is set off, the allergic manifestations clear up temporarily even though those patients are certainly not hyperadrenal. They have normal adrenal function when they get their disease.

Chairman Dorfman: It would be easier to discuss this if you would define what you mean by the alarm reaction.

Dr. Warner: By that I mean adrenalin acting primarily through the stimulation of the ACTH mechanism acting on the adrenal cortex giving out cortisone. Diseases such as rheumatoid arthritis have been successfully treated by psychotherapy for years.

Chairman Dorfman: I would have some hesitation in accepting the validity of some of these points. They are lacking in experimental proof. I wouldn't accept that it has been known for years that rheumatoid arthritis can be cured by psychotherapy. I have never seen a control series where one has proof that rheumatoid arthritis is a disease that responds to psychotherapy. The fact that a given patient responds does not prove the alarm reaction has been shocked and therefore the adrenal has been restored.

We have been looking very hard for an experimental basis for differences of adrenal responses. I wouldn't argue with Dr. Warner that the adrenal responds to stress, but I would argue that nobody has demonstrated that (1) the lack of this response is the cause of all of the diseases that we will be discussing and (2) that the response of diseases to the adrenal hormones is a result of substitution therapy. But we would not like to convey the impression that this is a closed subject, and that the views expressed are final.

One point Dr. Potts has mentioned deserves further amplification. That is the natural history of the disease being treated. There has been a great deal of argument about whether ACTH or cortisone affects the course of diseases in the sense of repression, or in termination in the manner which we observe with antibiotic therapy. The great mass of evidence at the present time points rather to repression, as Dr. Potts has mentioned, in the case of eye diseases. If you are dealing with a disease that is chronic, improvement occurs only while the drug is being administered. If you are dealing with a self-limited disease, for all practical purposes, an apparent cure may be obtained. This is quite important from the point of view of a number of diseases, particularly rheumatic fever. As you all know, rheumatic fever can have both of these courses. It can have a chronic, continually active course, or it can have an acute course. It is quite obvious then that the results of therapy might be expected to vary with different patients. Do you think, Dr. Rothman, this sort of thing is true in skin diseases?

Dr. Rothman: Yes, it is. Diseases which emphatically are known to be self-limited can be suppressed and if you continue therapy as long as the disease is supposed to go on, then you apparently have begun curing the disease from the moment that you start your hormone therapy. As soon as you start to treat diseases which have a more chronic course, a recurrent type of course, then you find that with withdrawal of the drug the signs recur. As a matter of fact, in the great majority of cases the relapses seem to be more severe than they would be in spontaneous course. Whether this is a true rebound phenomenon, and whether it can be proved statistically that relapses are more severe after withdrawal of the drug, I do not know, but this is my impression.

Chairman Dorfman: In trying to find the mechanism of action of hormones and other substances of biologic activity one of the most discouraging things is to try to find a biologic effect that can be studied. The situation with cortisone has been reversed. Most everything that has been tried has shown some change and it is therefore hard to determine which changes are most significant. Inhibition

of the inflammatory reaction can be demonstrated in a number of ways. Analysis of the nature of this inhibition suggests that a number of different processes may be affected. Adrenal-cortical steroids seem to have an important effect on the permeability of the capillary vasculature. The nature of this effect is at present unknown.

Dr. Potts: There is some evidence on this particular point afforded by studies of the eye. The eye is normally impermeable to a number of the antibiotics such as penicillin and streptomycin. The increased permeability of the inflamed eye to these substances is counteracted by cortisone therapy.

Chairman Dorfman: It is also well recognized now that there is an inhibition of the growth of connective tissue, including fibroplasia and formation of fibrous tissue. Whether this is primary or secondary to vascular changes is unknown. It should be pointed out that this inhibition is usually produced with rather large doses so that it does not necessarily represent a contraindication for the use of the hormones, and does not mean that the drugs can be used to inhibit scar formation. The question of the effect of hormones on antibody production is a complex one. The numerous studies of this question have produced variable results. Some of these have shown inhibition of antibody production while others have not. It has been shown in experimental animals that cortisone increases susceptibility to infection, although such infections may not be manifest with the usual signs. This is consistent with the clinical finding of an increase in intercurrent infections. This is one of the dangers of their use, although it can frequently be obviated by using prophylactic antibiotics. This is important because of the question that has been raised of using these drugs to overcome the toxicity of infection. I don't know whether this has been done in dermatology as in other fields.

Dr. Rothman: In acute infections no one would think of giving ACTH or cortisone. It is generally accepted now that acute infections are contraindications for the use of hormones, however, a most important consideration is whether the morbid process endangers life or not. If it does and cortisone or ACTH may be life-saving, their use is imperative even if one fears the risk of infection.

Chairman Dorfman: We would agree that the abolition of toxic signs of infection certainly would not be an indication of giving the drugs and that the presence of infection would usually be a contraindication.

Dr. Rothman: Yes, excepting the immediate danger to life.

Dr. Potts: There is a great tendency for ophthalmologists to use something that is going to keep an inflamed eye from being red, whatever the cause. The case of viral diseases hasn't been mentioned. They occur significantly in the eye, and many cases of keratitis with herpes simplex virus can be completely masked as far as symptoms are concerned by the local use of cortisone. However, there isn't any effective agent against this disease. In experimental animals, eyes have been ruined without showing any signs or symptoms of the disease except actual tissue destruction.

Dr. Lawrence Breslow, Chicago: Many ophthalmologists have come to the conclusion that cortisone is the only drug needed. Adverse effects occur very rarely. Is this point that was just brought out a practical one? Is it one in a hundred, a thousand or 10 thousand?

Dr. Potts: It is a very practical one and was strongly emphasized at the recent meeting of the Academy of Ophthalmology. Treating infections with cortisone is not the best practice, and cortisone is not indicated at all until the diagnosis has been made. Then it should be used in noninfectious diseases.

Dr. Rothman: Does ACTH give an initial dramatic response in all cases where it is administered as it does in rheumatic fever?

Chairman Dorfman: There is some dispute as to the effect of ACTH and cortisone in rheumatic fever. At one extreme Dr. May Wilson at Cornell claims that early treatment of rheumatic fever results in termination of the disease. On the other extreme, there are those who believe that these agents have no value whatever. In between are several groups of workers, including our own, who have felt that administration of these drugs results in suppression of the manifestations of the disease. Here is the problem: If we have 100 children who enter a hospital with rheumatic fever and are not treated at all, a large percentage will have a spontaneous remission with little cardiac damage, and will leave the hospital in relatively good condition. A much smaller number continue, for some reason completely unknown at the present time, to have rheumatic fever. It is obvious that the results obtained with ACTH or cortisone therapy will vary with the type of patient selected. There are at least 2 other important questions with regard to rheumatic fever. If ACTH and cortisone are suppressive drugs, what advantage do they have over salicylates, and does suppression

during the acute phase affect the incidence of rheumatic heart disease? As many of you know, there has been in progress during the last 2 years a cooperative study under the auspices of the American Council on Rheumatic Fever and the National Heart Institute attempting to answer these questions. Preliminary results so far have shown no differences in the acute course of patients treated with ACTH, cortisone and salicylates. There has not yet been sufficient time to determine whether there are any differences in the incidence of structural heart disease in the 3 groups.

Dr. Joseph F. Raffetto, Asbury Park, N.J.: What about the dosage of ACTH and cortisone? Do you find any difference between the two?

Chairman Dorfman: The results of the study so far have shown no consistent difference between the 2 drugs. This might be a good time to consider the general problem of dosage. The question of a proper dosage of either ACTH or cortisone is not entirely simple. There are as yet no data which permit the establishment of a relationship between dosage of ACTH or cortisone and body weight or surface area. In children above the age of 3 or 4 years, we have started using ACTH at a level of about 20 mg. q.i.d. Some variability has been occasioned in the past by inconstancy of potency of ACTH preparations. With the newer highly purified gel preparations, administration twice a day seems to be effective. This average starting dosage should be subject to some variation depending upon the severity of the disease, and to some extent upon body size. This initial large dose is decreased in a stepwise fashion to the minimum dosage which will maintain clinical remission. It appears to be wise to withdraw therapy gradually. The amount of cortisone necessary is about 2½ times that of ACTH. Cortisone may be administered by mouth every 6 hours. When given intramuscularly, at most, it should be given twice a day and usually once a day is sufficient.

This dosage schedule is only an approximation, and will vary considerably with the nature of the disease, its severity and the individual patient. Thus while such a schedule might be used in rheumatic fever or rheumatoid arthritis, smaller doses may be adequate in the treatment of asthma. Dr. Rothman, would you agree with this dosage schedule?

Dr. Rothman: On one hand I would like to emphasize that there are certain effects which we never can achieve if we start with small doses. On the other hand, once the therapeutic effect has set in, the dosage should gradually be lowered to the "maintenance dose," meaning the minimal dose sufficient to decrease signs and symptoms of the disease. The maintenance dose is extremely variably in the same disease and it is also variable in time. We are sometimes able to keep a child with disseminated lupus erythematosus in complete remission with as little as 50 or 75 mg. of cortisone by mouth or comparable doses of ACTH, and then suddenly we find this is not enough; one has to go higher because fever occurs, sedimentation rate goes higher, general condition gets worse. If you treat such severe diseases as rheumatoid arthritis or disseminated lupus erythematosus you should start with high dosage. We have quite a few cases where we have much more difficulty in the further course of treatment if the original dosage was low.

Chairman Dorfman: Do you have any feelings about this dosage schedule, Dr. Potts?

Dr. Potts: Eye diseases that respond to systemic therapy are amenable ordinarily to 100 mg. of cortisone per day for adults if an initial dose of 200 or 300 mg. is given. That is often scaled down for children and good effect is achieved. The local therapy of the eye diseases which is so important is another matter. There are 2 preparations available for local therapy of eye diseases. One of those has 5 mg./cc., the other 25 mg./cc. of cortisone acetate in aqueous suspension. These are ordinarily used on the first day in a dosage of one drop to the affected eye once every hour, and can be tapered off to once every 2 hours and then 4 times a day as a therapeutic effect has been reached.

Dr. Jacob: In my experiences, many times just 5 units difference made a great difference.

Chairman Dorfman: I would agree with that, and that is one of the reasons why I have been squirming a bit about giving specific doses. What I meant really was just a starting level and then you must adjust the dosage, as you stated.

New Speaker: In talking of dosage in small infants, I wonder if Dr. Potts would comment on the retrolental fibroplasia. Is it all local therapy or systemic therapy with local?

Dr. Potts: Studies on retrolental fibroplasia have been run, using dosages of ACTH 5 to 20 mg./kg./day in premature babies, and have not shown this therapy to be effective. What is worse, there has been an increase in the number of deaths in this series as compared with a comparable control series, which investigators attribute directly to infection fostered by use of the ACTH. Now, even in these extremely high doses where body growth was inhibited, and where these extra deaths occurred, there was no demonstrable effect on retrolental fibroplasia.

Chairman Dorfman: An important question is the whole problem of maintenance therapy. It is a complicated one and particularly when you are treating rheumatoid arthritis. Many physicians with a great deal of experience are less and less sure about maintenance therapy. When you are treating a patient who is chronically ill, a state is reached in which a compromise must be made. For a short period the patient may be treated with a large dose and dramatic relief obtained. Such large doses quickly result in signs of Cushing's disease. As doses are decreased symptoms of disease return so that a nontoxic but therapeutically successful dose cannot be found. It is then frequently necessary to accept only partial alleviation of symptoms. In other patients apparent therapeutic effects are obtained at lower levels, but one must be cautious that these do not represent spontaneous remission.

Question: What do you consider adequate studies for following a patient on hormone therapy?

Chairman Dorfman: One of the things one should follow particularly is the body weight, because it is a very good simple index. The blood pressure should be measured. Now, as far as the chemistries are concerned, when a patient is on a large therapeutic dose we do pH, CO_2, and sodium and potassium, if possible at weekly intervals. At a smaller dosage level this is not necessary. In the case of nephrotic patients these tests should be followed at closer intervals, and the body weight should be followed daily. Blood pressure should be followed daily.

Dr. Rothman: I do not know whether there is any difference between children and adults. We don't get into trouble with hyperadrenalism if we do control body weight, blood pressure and test the urine for glycosuria, and we are careful if we do get glycosuria. We do not do eosinophil counts anymore. One important point which has nothing to do with laboratory tests is the behavior. How does the patient feel? If the patient feels extremely well and happy, I'm concerned; euphoria is a very early sign of undesired hyperadrenalism.

Chairman Dorfman: Our experience isn't too different, except that I will say the emotional changes are much less common in children.

Dr. Rothman: Do they have fewer psychoses?

Chairman Dorfman: Oh, yes, as a matter of fact, aside from the series of patients who have had convulsions, we have seen virtually no psychoses in children.

Dr. Jennings: Is there any particular advantage of cortisone over ACTH?

Chairman Dorfman: We do not have time to go into this question adequately from a theoretical point of view. Practically speaking, cortisone has the advantage of being cheaper and easier to administer. There is some evidence that in the acutely ill patient a more prompt response is obtained with ACTH.

Dr. Potts: There is another theoretical point that probably ought to be emphasized. Cortisone itself may not be the adrenal hormone even though it is perhaps converted to the hormone in the body.

Chairman Dorfman: There is some reason to believe that compound F or hydrocortisone which has recently become available may be more physiologic. Recent reports indicate that it is much more active than cortisone when injected directly into the joint.

Dr. Breslow: Is there any danger that ACTH in the child depresses the other functions of the pituitary?

Chairman Dorfman: This has largely been a theoretical danger. It has been suggested that there is such a danger. There is as yet no evidence that this really occurs. I would like to mention one other thing about hormone therapy. On the large doses most people now prefer to restrict sodium intake to at least something under 2 gm./day of sodium chloride and to give 2 to 4 gm./day of added potassium chloride. Some investigators prefer potassium acetate.

In this second portion of the presentation we would like to speak more of specific diseases. We might start out with Dr. Rothman telling us about specific skin diseases in children.

Dr. Rothman: The first disease I would like to mention is bullous erythema multiforme which is sometimes called Stevens-Johnson syndrome. We all know that there are cases of erythema multiforme which endanger life. The child has very high fever and extremely severe eruption of the skin and of the mucous membranes, with marked toxicity. The effect of ACTH and cortisone is dramatic in this disease. It cannot be claimed that these drugs do prevent later recurrences, but we have a couple of cases where I feel strongly that these drugs have been life-saving. This brings me to a schematic division of diseases in regard to indication for these hormones, namely, diseases where there is an acute danger to life, or the nature of the disease is such that in great probability

it will have a fatal ending. Now, in pediatrics, in addition to these cases of erythema multiforme, acute and subacute disseminated lupus erythematosus does belong in this group. Although the management of this disease even with ACTH and cortisone, is rather difficult, these hormones are absolutely indicated in this disease because a hyperacute attack of lupus erythematosus with a high fever, with severe signs of the disease such as extreme leukopenia, high sedimentation rate, marked shift of plasma proteins, urinary findings, etc., will, almost invariably, end fatally. There can be very little doubt that we can get over several such hyperacute attacks with ACTH and cortisone and in some fortunate cases the patient goes into a remission so that the patient does well with no therapy at all for many months. We have had fatalities in cases of lupus erythematosus, but I don't remember a single case where there was no response at all, although in some relatively poor responses have been observed. The results are not as favorable as with pemphigus vulgaris (which is not a childhood disease). In pemphigus we have not lost a single patient so far. A third disease is dermatomyositis. My experience with ACTH and cortisone is not very favorable. Their effect in this disease is not comparable to their effect in disseminated lupus erythematosus. I want to mention that dermatomyositis has been treated very successfully in the last few years with testosterone. Experience with cortisone and ACTH in the treatment of periarteritis nodosa has not been favorable. In diffuse progressive scleroderma when it affects the lungs and gastrointestinal tract the results have been striking. But, in the long run, we haven't seen any really permanent effect and particularly no effect on the skin. Because of data on sudden deaths following ACTH treatment in scleroderma we have completely stopped using these drugs. In cases of so-called linear scleroderma, which start in early childhood, we haven't seen any effect of ACTH or cortisone.

Now, to go on to the next group, that is, the nonfatal or self-limited diseases: here the question comes up as to whether one should use these drugs in order to make the patient more comfortable. These are such diseases as atopic dermatitis, contact dermatitis and urticaria, in which the patient may be extremely uncomfortable for many days or possibly for a couple of weeks. I feel that, as in the nonfatal chronic diseases, this is more a matter of moral or social considerations than a medical question. You do what you think is best. I don't use these drugs because I get along with more harmless measures. If I had a very acute case of laryngeal edema in an initial attack, of course I would give ACTH.

Dr. Jennings: Is there any reason to think these drugs change the long term courses of eczema?

Dr. Rothman: I'm afraid I'm fatalistic in that respect. Nothing can change the course of an atopic infantile eczema. The only thing which really changes the whole situation is a very abrupt change in environment. ACTH and cortisone seem to be effective in psoriatic arthritis, which, according to newer work, is a definite entity. It is more or less restricted to the proximal joints of the hands and feet, and there are slight specific histologic findings on biopsy, extensive necrosis. Apparently much higher doses are necessary to influence the psoriasis. I never would treat psoriasis without arthritis with ACTH or cortisone. We can clear it up with ultraviolet light and local applications.

Dr. Breslow: Do you consider hypertension in lupus erythematosus a contraindication?

Dr. Rothman: It depends on the kidney findings. If the hypertension is a sequence to renal disease, then of course you do regard it as a contraindication. In my experience you don't get very good results if the renal disease is advanced.

Chairman Dorfman: We might now consider the present situation as far as the use of these drugs in renal diseases. You are all, I am sure, aware of the large number of reports which have been concerned with the use of the hormones in the nephrotic syndrome. We are speaking now with no particular prejudice as to whether the nephrotic syndrome is a separate entity, lipoid nephrosis, or a stage of glomerulonephritis. It is the impression of most investigators that similar results are obtained with both groups of patients. Data collected at several institutions indicate that a diuresis by ACTH can be induced in 60 to 70% of patients with nephrosis. In the original work it was observed that there is at first an increase in water retention, an increase in weight, and then later a diuresis, which was first attributed to a withdrawal of ACTH. As more experience has been gained, it has been found that diuresis frequently occurs while the drug is being administered. This diuresis is accompanied not only by a loss of the edema, but frequently by other signs of remission of the disease such as a drop in albuminuria and a drop in the blood lipid content. After diuresis has occurred, some patients will gradually reaccumulate edema and go back to their previous state. In some instances treatment may be repeated several times with similar results. Other patients will

apparently stay in remission for a longer period of time. It is hard to assess whether this is due to spontaneous variation in the course of the disease, or whether the course has been changed by therapy. Some patients will not have a diuresis as a result of the first course of therapy, but may get response to a second or third course. A major question involves the problem of whether this represents only an interesting phenomenon or a really worth while form of therapy. At the present time my own opinion is that it is worth while therapy, although in certain patients the repeated reaccumulation of fluid may require abandonment of this treatment. Cortisone, which was originally thought to be ineffective in nephrosis, has now been reported to duplicate the effect of ACTH. Although adequate comparative studies are not as yet available, ACTH remains the drug of choice.

An important problem in the case of nephrosis is the presence of severe hypertension and markedly diminished renal function. These findings are contraindications to ACTH therapy. In the case of acute glomerulonephritis or chronic glomerulonephritis, originally reported to be beneficially affected, present indications are that they are not amenable to treatment with ACTH and cortisone. There have been some suggestions that these diseases may be affected in an undesirable manner by these hormones.

We might turn now to a discussion of the treatment of specific eye diseases with ACTH and cortisone.

Dr. Potts: The star example of all is acute nongranulomatous anterior uveitis characterized by increased protein in the anterior chamber but no large amount of precipitates on the cornea. This condition is confined almost exclusively to postadolescence. There is something like a 50% response to local cortisone treatment. When one is treating a granulomatous disease, one does not want to spread the systemic granuloma by using systemic therapy in the eye, so that one is restricted to local therapy or nothing if systemic granulomata are present.

The second disease is interstitial keratitis. Again, the response is dramatic and the formation of deep vessels in the cornea, which is characteristic of the disease, is thoroughly inhibited. Some caution has been expressed due to the finding that the disease seems to flare up in an unmanageable sort of way after cessation of cortisone treatment. There are not enough cases to judge as yet, but in spite of this early dramatic response perhaps interstitial keratitis should be viewed with considerable more caution when one institutes even local therapy.

Dr. Rothman: If you have started treatment, do you go on or do you try to stop treatment?

Dr. Potts: Ordinarily, up to the present time, we have been going on because the disease is so inexorable.

Dr. Julius Margolis, Coatesville, Pa.: What do you think of the use of penicillin?

Dr. Potts: In the days before cortisone, penicillin was of no value whatever, and in the absence of active syphilis we have not been encouraged to use it in connection with cortisone, not believing it would have any significant effect.

The effectiveness of cortisone in marginal ulcers is quite good. In a nonspecific ulcer, etiology unknown, the inflammation has always been found to be secondary, never primary, but possibly due to a hypersensitivity reaction. The therapeutic result is good.

The question of corneal grafts is important in adolescence. Corneal grafting for interstitial keratitis is often a treatment of choice and corneal grafts do take well. Cortisone has been suggested for the inhibition of the pseudosensitivity reaction which apparently occurs even in transplants from person to person. Against this possible advantage, one must balance the inhibition of fibroblastic proliferation which has been adequately demonstrated both in cataract sections and in transplants in experimental animals. Whether to use cortisone in modified amounts to prevent neovascularization of the corneal graft, and to prevent the hypersensitivity that is believed to occur is still open to question.

There is no question about chemical burns, because in this case, except in the most severe ones, there is no need for fibroblastic proliferation in repair of the cornea. Most of the stroma remains intact. The superficial layers of the stroma are damaged and the epithelium is removed. Since epithelial proliferation is not inhibited the indication for treatment of chemical burns is clear.

Question: How long after sustaining a chemical burn to the eye would the use of cortisone be helpful?

Dr. Potts: I would say that it ought to be started pretty quickly.

Question: In terms of hours, days?

Dr. Potts: One ordinarily sees a chemical burn within the first day.

Question: Then, if it weren't started immediately it wouldn't be of very much use?

Dr. Potts: No, I would think that at any time before the state of complete scarification it would be of some use, but there would be a variation in effectiveness depending upon how long the reactive process had taken place. Of course you have to remove the offending agent as the first step. If there is any question of chemical substance remaining in the eye one would have to get rid of it before thinking of any other type of therapy.

In bacterial disease it has been suggested that cortisone plus antibiotics be used to relieve the patient of all symptoms. This is not really indicated because numbers of bacteria are now antibiotic-fast. Consequently, cortisone might interfere with a recognition of failure of antibiotic therapy.

Chairman Dorfman: It might be wise to point out that this same general situation obtains with regard to generalized infections. In view of the masking effects as well as the apparent decrease in body defenses, it would seem unwise to use ACTH and cortisone to treat toxic symptoms of infection.

Dr. Levinson: In vernal conjunctivitis what strength solution do you use?

Dr. Potts: Either of the suspensions, once every hour for the first day would be adequate. The thing that I didn't mention was that the full strength 25 mg./cc. material has a fairly high concentration of benzyl alcohol. It is sometimes irritating, particularly to children, and for that reason it might be worth trying the lower strength.

Chairman Dorfman: We ought to discuss certain specific pediatric entities in which these drugs have value. We might start with a consideration of various hypersensitivity states. Among these are acute drug reactions, particularly those due to penicillin. There should be no question about their use in acute edematous reactions which may threaten life, such as acute laryngeal edema. In this situation the drug of choice is ACTH because of its prompt action. There is no problem of long term therapy since these conditions are usually self-limited. It is a short-term, acute, emergency situation. I would feel that if the disease process can be controlled with drugs that are easier to use, cheaper and safer, the hormones should not be used. This problem is faced particularly with asthma. There certainly seems to be no question that asthma responds dramatically in a large percentage of cases. In severe intractable asthma, which may be life threatening, there should be no question that ACTH or cortisone should be used. The duration of therapy required in asthma is highly variable. A large number of patients are apparently benefited by a few days of therapy, and remain free of symptoms for some time. Others require almost constant therapy, or at least frequently recurring courses of therapy. What this means in terms of the mechanism of the drugs or whether here again is the question of whether the disease subsides itself is not known. The dosages required may sometimes be reasonably small.

We might now go on to the discussion of hematologic disease. Most of my information is derived from Dr. Mila Pierce of Bobs Roberts Hospital who has had a great deal of experience along these lines. As far as malignancies are concerned, there seems to be a uniform agreement now that only acute leukemia shows response to hormone therapy. About 65% of untreated patients develop a remission of their disease on treatment with ACTH or cortisone, ACTH being apparently more effective. This remission, however, is usually short-lived, but can frequently be reproduced a second time, less frequently a third time, and practically never more than 3 times. While it serves to prolong life in these children, the longest any of them have survived is about 20 months. Occasionally patients first get a remission with these drugs and still get another remission with aminopterin, or vice versa, but the eventual fatal termination has not been prevented. Of course, no one is very optimistic that any patient's life is going to be saved by any of these treatments. As far as the other types of lymphoblastoma are concerned, ACTH and cortisone seem to be ineffective in Hodgkin's disease or chronic forms of leukemia.

There are 2 other hematologic conditions which are reasonably common in children which bear mention. There are now a number of reports indicating that treatment of thrombocytopenic purpura results in a rise in platelet counts and cessation of the bleeding tendencies in a large percentage of cases. Present evidence does not suggest that hormone therapy is a substitute for splenectomy as a final treatment for the disease, but that in acute forms of so-called secondary thrombocytopenic purpura which may result from infection or drug administration, which are self-limited, this may be a very satisfactory treatment. In so-called primary or essential thrombocytopenic purpura this therapy should probably be considered only a temporary measure. The situation with aplastic anemias is almost identical, that although the percentage of patients that respond is somewhat smaller, you do get

response in aplastic anemias of a number of varieties. Occasionally in acute situations this may be a useful form of therapy. In other more chronic forms it becomes difficult to handle. The patient continues to have aplastic anemia. You may decrease the required number of transfusions, but the underlying disease remains. There have been several reports on the effectiveness in transfusion reactions, although not for the renal component.

Question: Is there any comment on erythroblastosis?

Chairman Dorfman: There have been a number of suggestions that erythroblastosis should be a disease that responds to hormone therapy since it is dependent on an immunologic mechanism. Two different methods of use have been suggested. The first is the treatment of the mother to prevent sensitization while the other involves treatment of the infant to prevent the antibody-antigen combination from destroying the red cell. As far as the second, we have had no experience with it. There are a few reports in the literature on a very small series of cases. At the present time most people interested in the problem of erythroblastosis are so much more interested, and are having so much greater success, with multiple exchange transfusions that it hardly seems valid to switch over to this form of therapy. There has been one small series in which the mother has been treated and the results are not very impressive. The theoretical idea remains but practical knowledge isn't available.

Chairman Dorfman: We might summarize briefly by saying that there has been now a very wide swing of opinions about the variations of the values of these drugs. Originally there was great enthusiasm about their use in all sorts of conditions and now some people are beginning to be much less optimistic. Some people have expressed opinions that they are valueless. It is quite clear that we all agree that neither extremes represent a picture. If we accept these agents as new therapeutic tools which have very specific uses with advantages and disadvantages, they become valuable additions to our means of treating disease in children, occasionally life-saving, more frequently palliative.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussions could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE two home medical care programs* described below are attempts to expand the teaching of medical students and house staff beyond the hospital walls into the home and community. The need for this expansion is a matter of sharp debate. On the one hand are those who point to the heavy load of the present curriculum and to the high level of current clinical teaching and research. These people say that the chief aim of medicine is to study, diagnose and treat disease and this objective must not be diluted by concern with such things as health supervision and the influence of socio-economic factors in the home and community. These things can be learned after the physician starts practice.

On the other side are those who believe that the changing content of medical and public health practice requires some addition to present teaching and research and that this is best accomplished in a family care program. They point out that the work of the clinician and of the public health officer is coming closer and closer together. The content of medical practice has changed and is changing so that approximately half of the time of the general practitioner, the internist, the pediatrician and the obstetrician is concerned with normal physiology and with emotional stresses which are so common and predictable that they too must be considered normal. Most of our knowledge of physiology and of emotional stress has been developed around the patient in the laboratory and in the hospital. As students and practitioners, we need more knowledge about the individual in his family and community.

* These 2 papers are part of a symposium given at the 1953 annual meeting of the American Public Health Association and are published through the courtesy of the *American Journal of Public Health,* concurrently with publication in that journal. The paper by Dr. Bakst is slightly abbreviated here; the full text will be given in the *American Journal of Public Health.*

The public health officer is still primarily responsible for such mass activities as the prevention of epidemics and the provision of safe food, water and waste disposal, but more and more he is joining with the clinician to provide individual services for those well mothers and children, for crippled children, for old people and others who need such services and cannot get them without some planned program.

The attempt to teach these things didactically has a long record of mediocrity. A family care program will tie this teaching to a service and research activity which may stir enthusiasm and give it life. But a family care program will bring problems of some magnitude, it will cut across present organizational lines, it will combine the work of the general practitioner, the internist, the pediatrician, the psychiatrist, the health officer and others; it will require a kind of cooperation between these groups which is not common. It may offer high rewards to patient, student and practitioner.

DOMICILIARY MEDICAL CARE AND THE VOLUNTARY TEACHING HOSPITAL*

By HENRY J. BAKST, M.D.†
Boston

THE Boston University School of Medicine and the Massachusetts Memorial Hospitals have been concerned with the provision of medical care for the needy and medically needy for many years. A home medical care program was instituted as a joint activity of these two institutions in 1875. This program continued under the supervision of the Department of Medicine of the School of Medicine until 1948 when this responsibility was transferred to the Department of Preventive Medicine. The Professor of Preventive Medicine is Director of both the Home Medical Service and the Outpatient Department and also a member of the medical staff of the Hospital. This association of appointments allows a centralization of authority and control which makes possible a fairly intensive integration of services and continuity of medical care as well as a correlated field experience in medical practice.

The administrative and organizational aspects of this activity have already been described in considerable detail.[1] This will be reviewed briefly. Senior students in groups of 4 to 6 spend 4 weeks on the Home Medical Service. They provide medical care under the supervision of two full-time second- or third-year residents and the staff of the Department of Preventive Medicine. Consultations are available without charge from any of the special services of the Massachusetts Memorial Hospitals. Calls are received in the Home Medical Service office in the Outpatient Department daily from 8 A.M. to 3 P.M. A graduate nurse screens all calls, collects preliminary identifying data, determines patient eligibility, instructs students in nursing techniques, and is responsible for equipment and supplies. Routine laboratory procedures are performed by students including bacteriology, which is supervised by a member of the Department of Micro-

* This program is aided by a grant from The Commonwealth Fund.

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biology. Pediatric conferences are held twice monthly. Psychosomatic and medical-social conferences are held weekly.

Patients are hospitalized at the Massachusetts Memorial Hospitals, depending upon bed availability, or at the Boston City Hospital. Emergency dental service is provided by the Dental Clinic of the Massachusetts Memorial Hospitals. Bedside nursing care is supplied by the Visiting Nurse Association of Boston. Students carry a minimum supply of simple medications which are provided by the Hospital. Prescriptions may be filled at the Hospital Pharmacy. Housekeeping services and appliances are obtained from community agencies by the Social Service Department.

The service district is approximately one square mile in size. It contains a population of varied racial backgrounds numbering 50,000 and includes the greatest portion of the lowest economic stratum of the city. Home medical care is supplied on request to the needy population in this area which surrounds the hospital and medical school. This Service provides care for about 5,000 patients annually. Teaching and organizational responsibilities make it difficult to handle acute emergency situations effectively. These are referred to the emergency ward of the Boston City Hospital. Since better than 95% of the expectant mothers of the City of Boston are hospitalized for delivery, obstetrical experience in the home is largely accidental and very limited. Patients accepted for medical care by the Home Medical Service must meet the financial limitations established by the Hospital Council of Metropolitan Boston in respect to eligibility for admission as an outpatient. The upper limit of eligibility for a single person is $40 weekly. According to the preliminary data provided by the 1950 census, this standard makes 38% of the population of Boston eligible for home and outpatient care. The eligible percentage in the service district is considerably higher.

There are some interesting data relative to the patient population of the Home Medical Service (table 1). Over 48% of the patients seen for the 12 month period from

TABLE 1

PERCENTAGE OF PATIENTS IN SPECIFIC AGE GROUPS FOR HOME MEDICAL, INPATIENT AND OUTPATIENT SERVICES, MASSACHUSETTS MEMORIAL HOSPITALS

	Massachusetts Memorial Hospitals			
	Home Medical Service Nov. 1949–Oct. 1950	Outpatient 1950	Inpatient 1950	Population City of Boston 1950
Under 5 yr.	48.32	10.23	15.25*	8.0
5– 9 yr.	16.66	6.66	4.51	6.87
10–14 yr.	3.5	5.41	2.2	5.97
15–24 yr.	6.45	21.9	12.37	15.89
25–34 yr.	5.87	19.3	17.01	15.65
35–44 yr.	5.26	11.9	12.8	13.8
45–64 yr.	7.84	16.7	22.66	23.48
65 yr. and over	5.6	7.9	13.2	10.34
Median age (yr.)	5.3	28.9	34.2	33.5

* 11.4% newborn which if excluded raises the median age to 42.9 yr.

TABLE 2

PERCENTAGE OF PATIENTS IN VARIOUS RELIEF CATEGORIES: HOME MEDICAL SERVICE, MASSACHUSETTS MEMORIAL HOSPITALS, APRIL 1950 TO MARCH 1951

Category	% of Patients
Nonrelief	64.58
All Relief Groups	35.42
Total	100.00
Aid to Dependent Children	15.2
General Relief	11.8
Old Age Assistance	6.8
Veterans' Assistance	1.55
Aid to Blind	0.07
Total	35.42

November, 1949, to October, 1950, were under 5 years of age, 65.5% were under 10 years of age, and 13.4% were over 45. Comparable figures for admissions to the Massachusetts Memorial Hospitals (a 400-bed general hospital including communicable disease) for the calendar year 1950 are given. It is reasonable to assume that the hospital, the outpatient department, and the home each reflect a somewhat different aspect of the distribution of the burden of disease in the community.

The economic status of patients for whom home care is provided is rather difficult to evaluate precisely (table 2). Of the 15,173 home calls made in the 12 month period from April, 1950, to March, 1951, 64.58% of the visits were made to medically needy individuals. These patients did not exceed the limit of income eligibility established by the Hospital Council of Metropolitan Boston and were not receiving financial assistance from any social agency. Of the total number of visits made 35.42% were to individuals who were totally needy and were receiving financial assistance from a public welfare agency.

With the exception of those circumstances previously noted, the Home Medical Service makes a call to any patient who requests medical care if he cannot come to the Outpatient Department. Medical care is continued at home as long as it represents the most

TABLE 3

NUMBER OF VISITS PER PATIENT IN VARIOUS RELIEF CATEGORIES: HOME MEDICAL SERVICE, MASSACHUSETTS MEMORIAL HOSPITALS, NOVEMBER 1949 TO OCTOBER 1950

Category	No. of Home Visits per Patient
Nonrelief	2.86
Aid to Dependent Children	3.1
Veterans' Assistance	4.0
General Relief	4.1
Old Age Assistance	5.6
All Patients	3.25

satisfactory mode of treatment insofar as the patient is concerned. With these limitations for the 12 month period from November, 1949, to October, 1950, 84.23% of the patients seen by the Home Medical Service were treated at home, 8.83% were referred to the Outpatient Department for further evaluation, and 6.94% were admitted to the hospital. The services which are provided are essentially those which would be provided by a general practitioner or family doctor. It is believed, and has often been stated, that the general practitioner is qualified to care for 80-85% of all patients.

One may justifiably show some concern as to the volume and extent of medical care required by the patient population of the Home Medical Service. A partial answer to this question is provided by the number of visits made per patient in various categories (table 3). In the 12 month period from November, 1949, to October, 1950, each patient received 3.25 visits. This number does not appear to be excessive and is believed to compare favorably with the experience of other medical care activities. The age group and the type of illness, however, effect this number considerably. The medically needy population group represents 64.58% of the patient load. Over 65% of this group are less than 10 years of age. These patients averaged 2.86 home visits. Patients on Old Age Assistance, however, all of whom are 65 years of age or more, received 5.6 visits.

Consideration of other health services emphasizes clearly the significance of age and prolonged illness in the provision of medical care. A review of experience with social service referral on the Home Medical Service for the first six months of 1950 indicates that the rate of referral to the Social Service Department is twice as frequent for patients with prolonged illness as it is for patients with short-term illness. During this same period, if the group under age 20 and the group over age 40 are arbitrarily selected, the results are particularly striking. In the group below 20 years of age, the rate of referral to the Social Service Department is 13.7 per 1,000. In the age group over 40, the rate of referral is 153.8 per 1,000. The utilization of nursing service follows the pattern indicated by social service experience. Patients referred to the Visiting Nurse Association for bedside nursing care are overwhelmingly those suffering from prolonged illness. The average age of a group of random patients referred to the Visiting Nurse Association by the Home Medical Service is 53 years. If only those patients referred to the Visiting Nurse Association on more than one occasion are selected, the average age proves to be 60. It is clear, therefore that even when dealing with a patient population which is strongly weighted in the direction of the younger age groups, the factors of increasing age and prolonged illness affect strikingly certain quantitative aspects of medical care.

Increasing and widespread interest in home care programs has raised the question of proper and desirable administrative relationships of such an activity. Experience has indicated that certain essential requirements of structure and organization should be included in order to provide acceptably complete and adequate service. These are:

1. The services and resources of a general hospital
2. Coordinated utilization of community resources
3. Centralized administrative responsibility
4. Integrated cooperation of professional personnel
5. Specific geographic limitation
6. Adequate financial support

It is reasonably clear that the quantitative and qualitative aspects of medical services provided by a home care program are to a large measure determined by the facilities and

resources of the hospital with which such a program is associated. In fact, the establishment of a home care service without hospital resources would so sharply limit the extent of available equipment, facilities, and personnel as to reduce the program to a superficial level of circumscribed and questionable community value. The fact that a hospital participates in such a program broadens considerably the usual and accepted functions of such an institution. Under these circumstances, medical and hospital services extend beyond the walls of the institution to make a very real and significant contribution to the health of the community.

The extent to which completeness of health service is to be provided by a home care program is dependent upon the coordinated utilization of official and voluntary health and social agencies for the benefit of patient care. This goal is best attained by the assignment of social service personnel to specific responsibility in the home care program. Such a step insures not only consideration of the social, economic, and environmental factors which may be associated with illness but also the utilization of such diverse agencies as the Visiting Nurse Association, the Health Department, the Family Society, the Society for Prevention of Cruelty to Children, and, occasionally, the cooperation of local court officials.

In general, home care by its very nature requires consideration of the patient as an individual in relation to his environmental milieu and as a social being. Medical care under these circumstances involves professional medical attention but also the coordination of the services of the visiting nurse, public health and school nurse, as well as the medical social worker. In fact, the physician, nurse, and medical social worker form a medical care team which together with the pharmacist, dietician, physiotherapist, occupational therapist, and special technicians make possible the provision of medical care of a comprehensive nature.

Governmental relief agencies in which federal participation is a factor make specific provisions for meeting a major portion of the cost of medical care. In those areas in which local health departments administer medical care programs, additional financial support is obtained from the local government. To this extent medical care for the needy is supported by tax funds. While these funds may not meet the full cost of providing medical care, a certain portion of this burden is being defrayed. The balance of the cost is met by charitable contributions, the use of endowment funds by voluntary agencies, and, in some instances, by grants from private foundations. However, the problem of medical care for the needy in our experience represents approximately one third of the problem since about two thirds of the patient load consists of individuals who are able to provide for ordinary day-to-day needs but who cannot meet the cost of medical care, the so-called medically indigent. Medical care for this group is being provided by the same organization as that for the totally indigent but the financing of the care of the medically needy remains an unsolved problem. The definition of medical indigency is not one on which universal agreement may be obtained. In some quarters, the necessity for organization for the provision of medical care for this group has been sharply questioned. It is entirely possible that additional information in respect to the cost and volume of services required by this group may lead to a reasonable and acceptable plan for social action.

The use of outpatient facilities in the process of medical education has been relatively common practice for many years. Home care programs have been adapted for this purpose for a much shorter period of time. Further development in this direction will

be delayed by certain essential and preliminary steps necessary to provide service and educational facilities of the same quality for homebound and outpatients as are usually available in most teaching hospitals on the wards. This will require additional financial support obtainable only with great difficulty from existing medical school budgets and funds available to voluntary hospitals.

In summary, some of the medical care aspects of the domiciliary program as a function of a voluntary hospital have been presented. Of particular interest are the altered position of the hospital in relation to the community as a result of this activity and the position which the home care program occupies in meeting community health needs. What are considered to be the essential organizational and administrative requisites of such a program have also been discussed. The need for differentiation between total indigency and medical indigency and the problem of financing the cost of medical care for the latter group has been given particular attention. Finally, it is evident that the services provided by a home care program must be shaped to meet the particular needs of a given community. It is hardly possible that any single pattern will be universally applicable.

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THE RICHMOND HOME MEDICAL CARE PROGRAM

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Richmond

THE Richmond Department of Public Health (since it came into being in 1909) has been charged with the responsibility of providing medical care for the indigent. In the interval from 1921 to 1941 this Department became a Bureau of Public Health under the Welfare Department. In the latter year it was re-established as an independent department. Under both systems it conducted a physicians' home visiting service as a part of its over-all medical care program.

In the summer of 1947 a series of incidents suggesting inadequacies in the quality of this visiting service caused the staff to re-evaluate it. Many inherent weaknesses were revealed. Spot checking of the records showed them to be sketchy at best. There was no continuity between the patient's home and hospital or outpatient care. Follow-up visits were not made routinely but only when requested by a member of the sick person's family. Frequently such return visits were initiated by nurses or social workers. Laboratory service was not provided. Payment for drugs on City indigent prescriptions were limited to 25 cents of the purchase price. There was no medical supervision of the

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physicians working in this service. As a consequence, the service was of poor quality. The long-standing cliché that these doctors were overpaid for what they did and underpaid for what they were expected to do was very true of the Richmond program.

As a result of this informal review a study of similar programs in other cities of comparable population was undertaken. Seventeen such cities were surveyed by questionnaire. The information so obtained seemed of doubtful value for it was obvious that very little was being done to provide medical care for the indigent on a systematic and economical basis. It became apparent that home care in Richmond was neither better nor worse than that provided elsewhere. These studies convinced the directors that a community-wide survey was necessary if the City was to be stimulated to support a comprehensive program.

In the fall of 1947 the Health Division of the Richmond Area Community Council (one of the oldest councils of social agencies in America) was asked to study the problem and to make recommendations for an adequate service. A committee was appointed and, after an intensive period of study, made the following recommendations:

1. That the City abandon the use of the six part-time physicians.
2. That it establish within the Medical College of Virginia three residencies in general practice, and that these residents work under faculty preceptors.
3. That a general practice clinic, to serve as a family doctor's office be established within the Admitting Clinic of the Medical College to be staffed by these residents and the faculty preceptors.
4. That the hospitalization and outpatient clinic program for the indigent be coordinated with the Home Care Service under a qualified director, in order that continuity of care be assured.

The new plan was designed to provide medical care of high quality through a program which would ensure continuity of home, ambulatory and hospital care. It was considered unique in that the service would function administratively under the Health Department, but would be closely integrated with the Medical College.

These recommendations were immediately acted upon by the Board of Health and transmitted to the Richmond Academy of Medicine, where they were heartily endorsed, and an immediate inauguration of the plan was urged. With the approval of the Board of Health, the Academy of Medicine, and the Board of the Richmond Area Community Council, the Health Department referred the program to the City Council, who appropriated additional funds and reallocated funds currently being used for the City Poor Physician, in order that the new service could get started.

With the approval of these groups definitive plans were begun to inaugurate the new program. Appropriate arrangements were made with volunteer agencies and the Medical College whereby auxiliary nursing, laboratory, housekeeping, and rehabilitation services would be provided. Unfortunately, staffing difficulties prevented an immediate start.

In the early winter of 1948 representatives of the Commonwealth Fund, on a visit to Richmond, became interested in the plan and invited the Director of the Health Department to send them a narrative review of the program, after which it was agreed that the City funds were not quite adequate and that a grant from the Commonwealth Fund could be arranged.

Recognizing the need for sufficient well-qualified personnel and that the program would be a demonstration of community planning in the field of medical care, it was presented to The Commonwealth Fund as a request for a research grant to assist in

financing during a demonstration period. When the grant was made, three objectives were outlined.

1. To demonstrate that medical care of high quality, giving continuity of service between home, clinic, and hospital could be provided by a public health agency to the indigent and medically indigent under a coordinated plan in cooperation with a medical college.

2. That the faculty, residents, interns, and students of the Medical College could be made aware of the problems of a home medical care service and the social aspects of the practice of medicine among low-income groups.

3. That in time, data might be collected which would be valuable from the research point of view, on the problems of home medical service.

The program was begun on April 1, 1949. After getting off to the disappointing and turbulent start usually found in new projects, it gradually settled down to a smoothly functioning unit. It was not intended that medical students be assigned to the program during the first year. However, this decision was changed and they were so assigned on December 1, 1949. Their enthusiasm and interest was immediate and great.

The medical staff consisted of a Clinical Director who had the faculty rank of Professor of Clinical Medicine, and two preceptors, or consultants as they have been called, from the faculty of the Department of Medicine. Three residents from the staff of the Medical College Hospitals were assigned on a two-month rotation basis. The students spent two weeks on this service as a part of their medical service during their senior year.

A well-qualified medical social worker was employed as a consultant to the program. Since the beginning this person has been responsible for the development of relationships with community agencies, consultation with staff and students, and teaching duties. She also supervised the other medical social workers of the program and coordinated the services of the Public Health Nurses.

While the Committee appointed by the Richmond Area Community Council had been studying the Home Care Service, another Committee of this Council was studying the facilities for institutional care of the chronically ill. This study revealed a severe shortage of beds for this purpose; that the turnover was very slow; and that the majority of beds was not accessible to the indigent and medically indigent group due to cost. Upon the recommendation of this Committee and in order to make the best possible use of available funds for hospital care, the Health Department reallocated its appropriations, effective July, 1950. In addition to acute hospitalization provided under contract with the Medical College of Virginia the reallocation provided convalescent care in two general hospitals (one for white patients, the other for Negro) and for care of terminal and chronically ill patients in approved nursing homes. Contractual agreements were effected with the above institutions at $7.00 and $2.50 rates per day. It was believed that by close supervision at the Medical College Hospitals and through discharge planning, it would be possible to transfer patients to chronic and convalescent facilities, or to The Home Service, with considerable saving in funds.

The plan also stipulated that patients, when their condition permitted, be admitted directly to these lesser facilities. Three objectives were thus cited for the hospitalization program:

1. More effective use would be made of existing facilities. Formerly, the Department had given lump-sum subsidy grants to four local hospitals, without benefit of administrative control of the use of these funds. With contractual arrangements, control of funds

could be maintained and patient-care could be integrated with other phases of the overall Medical Care Program.

2. The change would assure patient care in the facility most suited to meet the needs as determined by the patient's medical findings.

3. More effective use would be made of available funds, since the per diem rate in combined convalescent and chronic facilities is 40% less than that for hospitalization in the Medical College Hospitals.

Later an additional part-time physician from the Medical Department of the College was employed to investigate the status of the patients hospitalized in the Medical College Hospitals with an eye to expediting their removal to more economical surroundings, and to follow-up the patients hospitalized by the Program elsewhere. In order to provide further continuity of observation and care of the patients, this physician attended the regular case review conferences.

In 1950, City Council appropriated $25,000 for a dental care program based on a recommendation of another committee appointed by the Health Division, Richmond Area Community Council. With the addition of this service, the provision of complete care of the indigent and medically indigent was achieved.

Auxiliary services were used extensively to provide adequate home care for the patients. Arrangements were made early in the program whereby the Instructive Visiting Nurses Association gave nursing care. In the last year approximately 3,500 nursing visits were made by this agency. In this period the Family Service Society provided 10,755 hours of housekeeping service. The Sick Room Loan Chest, a Community Chest Agency, furnished on a contract basis hospital beds, wheel chairs, crutches, and the like, upon prescription by the attending physicians.

Early in the program it became apparent that many of the patients needed rehabilitation. Accordingly, plans were worked out whereby the Department of Physical Medicine at the Medical College and the State Department of Education, Rehabilitation Division, would provide these services. At present the Physical Medicine Department is providing evaluators and therapists. With the addition of these services, the program is considered to be well-rounded, providing all the basic needs for adequate home care.

In addition to the hospital facilities and auxiliary services enumerated above, all of which are essential to the provision of coordinated medical care in which continuity is believed to be of the utmost importance, quality of care in this program has been maintained through its relationship with the teaching institution. It is well established in American medicine that if you want excellent medical care the best place to get it is on a teaching service. This precept is generally accepted as the students are well supervised by qualified physicians and their work is thorough. Coupled with these attributes is an intangible quality which though difficult to describe is manifested in many ways, namely, the eagerness of the student for the new experience of actually being in charge of a patient in his home environment. They report that the experience gained on this service is invaluable. Many state that it is their first chance to assume responsibility; others state that it is their first opportunity to see the prosaic in medicine. All of this is largely due to the fact that the student is encouraged to assume the role of a family doctor and, more important, he gets a feeling of responsibility for the management not only of the medical aspects of the case, but also for the social and environmental factors concerned. There is no doubt in our minds that student participation is excellent insurance for the preservation of quality in medical care.

While on this service students and residents have become acutely aware of the social and economic factors involved in the practice of medicine. Through the daily conferences with the preceptors, social workers, and nurses they have gained a new perspective. By the time they have completed an assignment on Home Care, they have had many opportunities to see the influence of adverse social conditions on their plans for medical treatment.

Weekly one-hour conferences are held for the discussion of the cases already seen, especially those selected as illustrating some problem of medical or social care. These conferences are attended by all members of the program, representatives of the various agencies concerned with these patients, and either the Director or Assistant Director of the Health Department. Cases are presented by the students or residents and freely discussed by all. In addition, the Director of the Health Department, who is also Professor of Community Medicine in the Medical College, conducts a weekly seminar in which the public health aspects of the patients actually seen by the students are discussed.

In the spring of 1950 the effort to develop residencies in general practice evaporated as too few of the graduates were willing to take a planned two-year hospital service for this purpose. With the cooperation of the Professor of Medicine it was possible to rotate two junior assistant residents from the Medical Service through the Program for periods of 10 weeks, and the students were assigned to this service for three weeks instead of two.

In the year July, 1950 to July, 1951, 9,147 calls were made on 3,001 patients, an average of something over three visits per patient. A study of the latter six months of the period showed that, by diagnosis, the cases fell roughly into 13 groups: acute upper respiratory infections 40%, influenza and pneumonia 8%, measles 13%, mumps 4%, diarrhea and enteritis 2%, tuberculosis 3%, diseases of childbirth and puerperium 4%, diabetes 2%, heart disease 10%, intracranial lesions (chiefly vascular) 4%, allergic condition 3%, malignant neoplasms 3%, and accidents 4%.

Last year (July 1, 1951 through June 30, 1952) 9,674 visits were made on 4,006 patients, an average of 2.4 visits per patient. This was an increase of almost one visit per patient over the old district physician arrangement. A study of the period from March 17 through April 3, 1952, showed that eight students, working in pairs, who were assigned to the service at that time, saw 85 new patients and made 86 calls on old patients with a new problem, a total of 171 patients who received 571 visits, an average of 8 visits per day by each pair of students. In addition they were making calls on chronically ill people who are seen more or less regularly every week or two. As a sample, while on the service, in four weeks, one team of students saw 11 patients with acute upper respiratory infections; 6 with measles; 3 with lobar pneumonia; 3 with bronchopneumonia; 1 with diabetes mellitus; 4 with cerebral hemorrhage; 1 with heart failure; 1 with gastroenteritis; 2 with pulmonary tuberculosis; 3 with acute salpingitis; 1 dying with cancer; and a considerable number of other conditions.

Many questions have been asked with reference to the cost of the program. Visitors want to know whether or not the program is economical. This can only be answered by giving a concise review of the appropriations made for medical care in Richmond. The City's budget for its entire medical care program, which includes acute hospitalization, chronic care, nursing home care, dental care, outpatient department care and 80% of the cost of the home care program, is $350,600. The cost of the Home Care Program per se is $82,501. This latter budget item was agreed to by the City and the College after conferences in which it was brought out that the City was responsible for the actual pro-

vision of medical care and that the College was responsible only for that part of the program concerned with the teaching of students. After careful analysis, the following formula was arrived at: City 80%, College 20%. Actually, the per capita cost for this well coordinated medical care program is considered to be extremely low. For the current year the amount budgeted is $1.52 per person. The per capita cost of the Home Care Service is 36¢, while the cost of home care for the welfare population served during the past year was estimated as being $17.33 per case. The cost per visit during this period was $4.41. Comparing this latter figure with the figure given for the City poor physician system in the year 1949, at which time the cost was $4.59 for the mere visit of a physician without the auxiliary aids, we believe that the program is economical.

Further analysis of Richmond's Medical Care Program showed that the inauguration of an efficient Home Care Service and the contractual arrangements made with chronic disease, convalescent and nursing home facilities are the two major reasons why the Department of Health was able to function within essentially the same amount of money and yet give both a greater range and a greater volume of service. In the year 1948-49 the City provided 18,925 hospital days. In the past year the City, by using the appropriate facility for each individual case, was able to provide 36,100 days of inpatient care for essentially the same amount of money. This is not only economical from the monetary viewpoint but is vital to the community in that we have been able to provide care for the chronically ill who previously were not admitted by the government as a responsibility.

The economy in the Richmond program is safe-guarded in many ways. First, the admission rate to acute hospitals is held down through the use of Home Care and other institutional facilities. Further, with a coordinated nursing and social casework program, patients come to the attention of the program in the early stages of illness, which in turn make possible early diagnosis and treatment resulting in shorter episodes of illness. In addition the hospital stay is often shortened by early discharge planning and transfer to Home Care or to less expensive convalescent and nursing facilities. A member of the Medical Care staff serves as a coordinator and is responsible for follow-up of cases accepted for treatment in all inpatient facilities. By making ward rounds, discussing cases with residents and other house staff, he is able to suggest transfer when it becomes medically feasible. By participating in discharge planning, we have learned that excessive hospitalization can be avoided, particularly when the desire to keep an interesting patient is prevalent, as in all teaching institutions. This phase has been materially improved by the infiltration of former home care students and residents into the house staff. Their Home Care experience has made them aware of the objectives of the total program, the availability of other resources, and the over-all importance of early discharge. The effectiveness of a systematic attempt to control hospital stay is reflected in the reduction of 1,794 days of acute care between 1949 and 1952, while the same number of patients received this care.

On June 20, 1952, after three years, the Health Department and the Medical College were able to report to the Commonwealth Fund that the project was successful and that the two institutions would jointly assume responsibility for conducting it. In taking over, both agencies agreed that the program would be continued with the same staff. In these three years many changes have been made and the next few years will probably see many more.

In conclusion, the following observations seem justified:

1. The cooperative effort of the Richmond Health Department and the Medical

College of Virginia provides medical service of considerable continuity and at a reasonable cost for the indigent and medically indigent. The service begins with the onset of illness and continues to restoration to economic usefulness, or throughout chronic illness to death.

2. (a) Medical students, house officers, and physicians are afforded a heretofore unknown opportunity to see patients in surroundings and under the circumstances of illness as it is met by general practitioners, which many of them will later become. Experience is gained in the observation and care of patients with everyday problems as contrasted with the obscure diseases customarily seen on teaching wards and in many teaching clinics. It is suggested that such programs may overcome certain of the marked differences between medical training and actual practice.

(b) Students have the opportunity to see how one community attempts to solve the illness problems of this group of society. Since it appears likely that similar groups exist everywhere, these young men will be better equipped to participate in such efforts in their own communities.

(c) Younger physicians see that patients cannot be treated as so many cases of anything, a fact very clear indeed to any practitioner; on the other hand, it becomes obvious that the doctor must consider all facets of the individual's family and social status as well as the illness itself. With experience, many "crocks" change into pathetic old men with very difficult, but perhaps soluble problems.

(d) Public Health or Community Medicine as a part of the curriculum is presented to the students more forcibly and in a more interesting fashion when discussed over patients who are at that time under the medical care of these same students.

3. The high quality of medical care afforded the indigent and medically indigent in Richmond has been accomplished at a reasonable expense to the taxpayer. This has been achieved by coordinating the activities of the many agencies involved, by utilizing the available resources most effectively, and by maintaining a close administrative control.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

USE OF THE CHILD HEALTH CONFERENCE IN THE TRAINING OF MEDICAL STUDENTS

By ROBERT W. DEISHER, M.D.*

MANY medical schools during the past few years have been devoting an increasing amount of time to the study of children themselves rather than to children's diseases. This would seem to be a wise trend inasmuch as we know from the Academy of Pediatrics' *Study of Child Health Services* that a large proportion of children seen by general practitioners and an even larger proportion of physicians in pediatric practice are well children. This leads us to realize that the understanding of normal growth and development is extremely important and ways must be found to give medical students who will soon be seeing many well children in their practices a concept of the child himself as well as his diseases.

DESCRIPTION OF THE CLINIC

The University of Washington School of Medicine has been unusually fortunate in having a facility such as the Child Health Center in which to give students training of this type. The Child Health Center came into existence in the summer of 1947 when an agreement was reached by the Washington State Department of Health and the University of Washington to organize a child health demonstration project at the University of Washington which would provide complete well child care for children of resident students at the University of Washington. In the beginning the primary function was that of service. There were a large number of veteran students at the University of Washington, many of whom resided in the student housing area in which the Center is located. Since the majority were subsisting on quite a limited income it was felt that the service offered by the Child Health Center was much needed by this group and one they would be unable to afford on a private basis. In addition it was thought that such a project would provide a health center in which different phases of preventive pediatrics might be taught and demonstrated to qualified students. The third activity of the Center was to be research in the field of child growth and development.

Since its beginning the training activity at the Center has undergone several changes. Training during the early period from July 1947 to the fall of 1949 was limited largely to physicians and nurses from within the northwest area who spent one or two weeks at the Center for in-service training. The physicians were either public health physicians who were doing considerable preventive pediatrics or physicians in practice who felt a

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need for more training along this line. Nurses were largely field public health nurses who were doing parent counseling and well child work. There were also some University students who spent a brief period at the Center for the purpose of orientation in the concepts of preventive pediatrics. These students were mostly from the School of Nursing, though some came from the Graduate School of Social Work and the Department of Home Economics.

With the beginning of the new Medical School at the University of Washington a need was recognized for training medical students in growth and development of children as part of their general pediatric experience. The facilities of the Child Health Center seemed to be ideal for this. Since that time the teaching emphasis has shifted until now the most extensive course of training at the Child Health Center is that planned for medical students. Service has continued as an important function only insofar as this service is necessary to provide material for good training. Research is currently being done by certain members of the staff.

Staff

From the beginning the staff of the Center has been selected by representatives of the University and of the State Department of Health. At present it consists of two pediatricians, two public health nurses, a medical social worker, a nutritionist, a dental hygienist, a laboratory technician and an administrative secretary full time, and a dentist, a child psychiatrist and a psychologist on a part time basis. Each professional staff member has a teaching appointment in his respective department of the University of Washington except one public health nurse. She is on the staff of the Seattle-King County Department of Public Health and carries a generalized program in the district in which most of the student families live.

The staff work closely together and function not only as individuals but as members of a professional team. Perhaps this can best be illustrated by the description of a patient's routine clinic visit.

Patient Service

In order to be accepted for service by the Center it is necessary that one member of the family be enrolled as a full time student at the University of Washington. It is desirable that the course of a child's development be observed over as long a period of time as possible. Therefore, to be accepted at the Center a family must be planning to remain longer than one year in this area and must cooperate in keeping appointments. Children of the regular pediatric age group are eligible for care but most of those being followed are under school age. Before being given the first appointment at the Center all parents have a screening interview with the medical social worker in order to acquaint them with the general philosophy and type of service offered by the Center. At this time parents have opportunity to ask questions about procedures and practices not clear to them and to find out how to get help with special problems they may have. This interview also serves as an opportunity to obtain early knowledge of the family situation and of the child's needs which are of particular interest to the parents.

During a regular clinic visit a child is seen first by the public health nurse who aids the parent in taking the temperature, weight and height. Parent and child are then taken to the examining room by the public health nurse. There they are joined by the pediatrician and a three way discussion is held concerning the child. Suggestions are made, and

questions of the parent are answered. The public health nurse may plan with the mother to make a home visit later.

If the mother has questions about certain kinds of behavior the child is exhibiting and it is felt that the problem is of such a nature that a more detailed discussion is necessary, the mother is referred to the medical social worker. In case the child has a medical condition necessitating referral to another clinic or private physician, it is suggested that the mother discuss this with the medical social worker. Casework contacts are on a short time basis and where long time casework seems indicated or where the problem is unrelated to the basic function of the Center, the medical social worker assists parents to seek help from the community source most appropriate to meet the special need.

When a mother has many questions concerning the child's diet, menu planning, or budgeting, or if she demonstrates a general lack of knowledge in this area, referral is made to the staff nutritionist. In addition to cases seen on a specific referral the nutritionist makes a periodic dietary evaluation on each child.

If the child is two years of age or older, he is referred to the dental hygienist. She gives instructions about tooth brushing and proper care of the teeth. Later appointments may include a series of fluoride treatments. An appointment is made for the dentist to inspect the child's teeth and secure x-rays. Since the dental program is largely preventive no restorative work is done. When this is needed, however, referral is made.

An appointment is made with the psychologist who examines all children coming to the clinic and may do repeated testing of any child when such information would seem to be of value.

The psychiatrist may on occasion see a patient when there is question in the mind of other staff members but he serves largely in the capacity of consultant to members of the staff. A considerable portion of his time is spent in various research projects carried on by the Center.

Using these clinical facilities, a training program for senior medical students was planned. The general program has been in operation since the beginning of the first senior class at the University of Washington School of Medicine in 1949.

Medical Student Training

Training is done with small groups of medical students (usually 4 to 5) who spend approximately 40 to 45 hours each at the Child Health Center. This is somewhat over a quarter of the total pediatric time of the senior year. A student's program is carefully planned for the entire time he spends in the Center and this includes a variety of experiences.

Each new group of students is carefully oriented by the Center director who points out the place of preventive pediatrics in the total pediatric field. New students very often are totally unaware of the fact that as practicing physicians they will be seeing other than ill children similar to those on the hospital wards. The concept of a well child conference may not be new to them but it is usually thought of only as a health department function and not as something which is an essential part of everyday private medical practice.

The type of information obtained in a well child conference, the handling of various types of children's behavior exhibited at the conference and some of the questions frequently asked by mothers are mentioned. The general nature of a well child conference is

discussed and students are then familiarized with the examining rooms and the routine of operation carried out by the Center.

This initial orientation to the well child conference is extremely important. Only if it is presented in such a way that the student feels it is an important phase of his work as a practicing physician will he benefit fully from his clinical experience.

On subsequent periods spent at the Center, medical students are given selected patients to see. Before interviewing the mother the student is allowed time to read pertinent information in the chart relative to the social background of the family. The Center medical social worker is available to the student who may wish to discuss further aspects of this with her either before or after seeing the patient. No direct supervision is given during the conference between the mother and medical student and he takes as much time as he needs for this interview. By experience we have found the student derives more from the conference if he is allowed to conduct it without another physician being present since otherwise, invariably, the doctor-patient relationship between mother and student is lost. If immunization procedures are indicated these are performed by the student.

Following his interview with the mother and examination of the child the student returns to the conference room where both are discussed in some detail with the pediatrician. This provides an excellent opportunity to acquaint the student with various aspects of growth and development as they pertain to the age child he has just seen. In the few instances in which the child has exhibited unusual apprehension about examination or immunization and the procedure was postponed the possible reason for the child's fear is discussed. When viewed in relation to the particular child the material has much more meaning than it would otherwise have. For example, child nutrition is more meaningful when applied to the specific case at hand. The pediatrician may suggest that the student talk with the nutritionist in more detail about the situation being discussed or may suggest that the student and the mother see the nutritionist for a three-way conference.

On each afternoon that students are seeing patients the child psychiatrist is present for discussion of some aspect of the case relating to simple emotional problems or emotional growth and development. He may participate in the discussion in conjunction with the pediatrician or may discuss some phase of the case alone with the student in more detail. Here again the integration of psychiatric concepts of growth and development seem to be more acceptable to the student than in a less pertinent situation.

In addition to the interview and physical examination the student does a simplified developmental examination on each child seen. Both pediatrician and psychologist are available to help the student with the test and to aid him in interpretation of the results.

In addition to the opportunity to talk with mothers and examine children in the clinic, a number of conferences, seminars and informal discussions are planned while students are in the Center. A weekly psychiatric conference is held in which a child is discussed who is currently being seen at the Center and shows some evidence of an emotional problem. An attempt is made to select cases where the problems are of a nature that would be seen frequently in the office of a practicing physician and not those likely to be seen in a psychiatric clinic. Excessive night awakening, marked parental concern over thumb sucking, refusal to eat, difficulty with toilet training and enuresis are the types of problems likely to be discussed. Each case is briefly summarized by the Center pediatrician as to the nature of the presenting problem and the pediatrician's contact with the mother and child in the clinic. Members of the professional staff present additional in-

formation: the medical social worker gives social background information concerning the family and tells of any contact she may have had with the family relative to the current problems; the public health nurse tells of her home visit and any significant observations she has made at the Center; the nutritionist relates her experiences with the mother during any nutrition interviews that may have taken place; the psychologist gives pertinent findings concerning the child's psychological test and the dental hygienist discusses the child's dental health and behavior in the dental clinic if she has had opportunity to see him. On occasions where the child has had contact with school or nursery school, representatives from these groups are invited and may also contribute information.

Following this presentation the psychiatrist moderates a discussion in which questions relating to the case are raised by the students and staff. In discusing these questions the psychiatrist endeavors to bring out general concepts relative to emotional growth and development rather than those related only to the particular case. Consideration is also given to the role each staff member will have in handling the problem.

Seminars and discussions concerning questions frequently asked by parents, immunizations, common orthopedic problems, growth, accidents and other related subjects are given by the pediatrician. The pediatrician and nutritionist participate in a seminar regarding child nutrition. The psychologist demonstrates the administration of a psychological examination and gives some interpretation of the meaning of the results. Several films are shown which have proved valuable in giving a better understanding of some phases of child growth and development. The Professor of Pedodontics from the School of Dentistry meets with each group of students and discusses some of the common problems relating to children's teeth and aspects of prevention. The Director of the Maternal and Child Health Division of the Seattle-King County Department of Public Health also meets with each group and explains to them the organization of well child conferences throughout the county and various public health aspects of a well child conference.

During the past year each student has made a visit to the home of one of the families he has seen in clinic. Cases were selected by the staff on the basis of possible teaching value to the student. Arrangements for this visit were made by the student at the time of his conference with the mother at the Center. Whenever possible this visit was made early in the evening so the student might have an opportunity to see the father's part in the family unit. Following the home visit the student reported to the remainder of the student group his impressions of the home and of family relationships and their affect on the child.

After some orientation to the over-all purpose and philosophy of nursery school education each student spends an afternoon in the nearby nursery school. In this way he can observe for a short time the activities and group reactions of preschool age children.

Summary and Conclusion

A description has been given of the Child Health Center of the University of Washington, its staff and their functions, as well as the teaching program being conducted for medical students.

The student working in such a Center is better able to integrate some of the basic principles of pediatrics, public health and psychiatry, thus making these areas more acceptable and interesting.

The teamwork displayed by the staff who represent a variety of professional approaches

is often remarked on by students. They seem to realize at last the functions of a public health nurse, a social worker, nutritionist, and others as represented by the Child Health Center staff and to recognize that they as physicians can benefit in terms of better understanding of their own patients from similar relationships with people from other fields. Perhaps even more significant, they begin to realize the other important phases which should be considered in following the growth and development of each child other than the physical.

It has been indicated that for the medical student to derive maximum benefit from a Child Health Conference experience, his time must be allotted carefully to various phases of the program in operation. Then each student's time must be planned so that certain pertinent information is obtained or experience furnished. To cover the many aspects desired we are fortunate to have an organization such as the Child Health Center in which staff members from several different special fields cooperate in teaching the growth and development of a total child. It is suggested, however, that even with a less elaborate child health conference plan many of the same points can be made if sufficient time is given for the students and a smaller, but interested staff is provided.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

THE ECONOMIC VALUE OF PREVENTIVE MEDICINE

WORLD HEALTH DAY, April 7, 1953, has been marked by the publication of a World Health Organization pamphlet, *Health is Wealth*.[1] This is a abridgement of an unusually informative monograph by Prof. C.-E. A. Winslow of Yale, *The Cost of Sickness and the Price of Health*.[2] At the Fifth World Health Assembly, furthermore, a series of technical discussions were held on the theme "The Economic Values of Preventive Medicine." In these discussions, Dr. Winslow presented a paper[3] highlighting some of the significant facts in this field. Many of the statements in this paper are apt and timely.

"Economic values do not provide the only—or even the primary—inspiration for the world-wide campaign for public health. . . . It is men and women who are fundamentally of importance, not dollars. . . ."

Yet, in day-to-day activities of public health workers in a "tough and practical world," it is essential to convince peoples and governments that specific goals of health improvement can be obtained and their attainment is feasible within world economics. Thirty years ago, Hermann M. Biggs coined a slogan which is still carried as a motto by the New York State Department of Health: "Public Health is Purchasable, Within Natural Limitations a Community Can Determine Its Own Death-Rate." The following is an excerpt from Dr. Winslow's paper:

"The first and most obvious measure of the crippling effect of sickness on society is its influence on the length of human life. It has been computed that while a death at fifteen years or under represents a net economic loss to society, a death at the age of forty represents a net economic gain, and a death at sixty-five years represents a net economic gain more than twice as great.

"It certainly is a cause for grave uneasiness that while the life span in North Western Europe, North America, Australia, and New Zealand (the so-called 'developed areas,' comprising one-fifth of the population of the globe) had, a few years ago, an average life expectancy of sixty-three years, another group of 'underdeveloped areas,' including nearly two-thirds of the world population, had a life expectancy of only thirty years. This simple fact emphasizes in dramatic terms the major problem of the human race today. At the time of the American Civil War of 1861-65, it was said that this country could not continue to exist half-slave and half-free. Nor can the One World of to-morrow continue to exist half-rich and half-poor.

"The burden of premature death which we have been considering is, furthermore, only a part of the problem. Morbidity takes an even greater toll of our economic resources than does premature mortality. In countries with a short life span, the major factors in morbidity and mortality are of a kind that should lend themselves quite readily to control. It has been reported that in Southern Rhodesia the loss of man-power due to malaria amounts

to five per cent to ten per cent of the total labor force, with its heaviest incidence precisely at the peak period of agricultural production. In India it has been computed that malaria produces an economic loss of about $28,000,000 a year. In Egypt bilharziasis costs nearly $7,000,000 a year. In the Philippines one person in ten suffers from malaria each year, while one person in fifteen suffers each year from tuberculosis. The economic losses due to these two diseases alone are estimated at $33 a year for every person in the population.

"A major part of this heavy burden of disease can be readily lifted from the shoulders of the human race; and we have no lack of factual experience at our disposal to prove what can be accomplished to demonstrate its economic value. In the case of the mosquito-borne diseases, the economic returns due to control measures are, of course, particularly striking. The dramatic elimination of *Anopheles gambiae* from Brazil and from Egypt is familiar to us all. In Peru, DDT spraying in highly malarious areas reduced parasite indices to less than two per cent of their former values; and it was estimated that extension of this program to the whole country at a cost of $1,400,000 would reduce the malaria bill by $27,000,000. In the Philippines malaria control reduced school absenteeism from forty or fifty per cent daily to three per cent; and industrial absenteeism from thirty-five per cent to less than four per cent.

"In Ceylon the use of DDT was introduced in 1947 at a cost of about $0.22 per capita in the area treated. The death-rate *from all causes* varied from twenty to twenty-four per thousand population. In the three years after the malaria program was introduced, the death-rate from all causes fell to twelve to fourteen per thousand, representing a saving of fifty thousand lives a year. A labor absenteeism of from twenty-five to thirty-five per cent in the Transvaal, Natal and Rhodesia was reduced to less than one tenth of that amount; and regions of major agricultural and industrial importance have been opened up for active and fruitful development. In Haiti a WHO/UNICEF program for the treatment of yaws has returned a hundred thousand incapacitated persons to work and has increased national production by five million dollars a year.

"Such results as this have a direct and important influence on industrial and agricultural programs. It was recently reported at a Harvard Conference on Tropical Hygiene that a malaria-control program, carried out jointly by a company operating in Saudi-Arabia and the national government, reduced the incidence of malaria among the company's employees from two thousand cases a year to fifty-three. The program of DDT dusting cost $45,000 and the saving in medical and hospital care provided amounted to $152,000 in 1950 for the company alone. A large fruit company states that malaria control has effected a saving of a million dollars a year in its hospital costs and has halved the costs of housing, since it used to be necessary 'to build for five hundred laborers in order to have two hundred and fifty working the next morning.'

"From the standpoint of community psychology, the World Health Organization has been wise in choosing for major emphasis during the past two years simple and efficient procedures, such as spraying with DDT, immunization with BCG, and treatment of syphilis and yaws with penicillin, which make it possible to obtain dramatic and immediate results at minimum cost. It must always be remembered, however, that such intensive campaigns conducted against individual diseases for a short period of time are, in themselves, demonstrations and not basic public health programs. If they are not followed up, mosquitoes will breed again, new generations of children will grow up with no resistance to tuberculosis, and treponemas will return to the attack. . . .

"We must meet health emergencies as they arise; but we must do so in such a way as to promote gradual progress toward the ultimate ideal of a soundly conceived and adequately supported permanent public health service in every area of the habitable globe. . . .

"When the stage of progress has been reached where the public health machinery is beginning to operate effectively in the control of mass epidemics, the program must be expanded to include the promotion of maternal and child health; to nutrition; to housing, so grossly neglected in most countries of the world; to occupational hygiene which becomes day-by-day a more and more urgent problem with the extension of the Industrial Revolution to new areas of the Far East; and, above all, to the complex problems of mental hygiene which only now, at long last, are beginning to receive the attention they deserve. . . .

"In order that the program in a given area be sound, it must be planned to meet the needs of a particular locale; and it must be administered with the special skills which come from training and experience. Efficient public health service depends primarily on administrators. Actual studies of the daily routine of the health officer have shown that a very large proportion of his time is spent in dealing with problems which have no relation to the practice of medicine, but which call for organizing ability and skill in applying the principles of mental hygiene to the difficult task of fostering cooperative effort. . . .

"Public Health, like government, must, in the words of Theodore Parker, be 'of all the people' and 'by all the people,' as well as 'for all the people.' Health programs can only be truly effective with the understanding, the support, and the participation of the citizens. This is where the Health Educator comes into the picture. Today, the good Health Educator is no longer merely an expert at selling a finished product of expert thinking. He or she is far more concerned in working directly with the people themselves, as represented by their leaders, in educing from them intelligent cooperation in planning the program itself so that it becomes *their* program and not something imposed upon them from above. In this difficult task of bringing the gap between expert knowledge and local mores, the psychologist and cultural anthropologist are coming to play an increasingly effective role. . . .

"In planning our health programs we sometimes meet a real challenge as to the essential desirability of the goals we seek to attain. Certain population experts tell us that there are already too many people in the world; and that such successful health programs as that carried out in Ceylon (which has led to an increase of two million in the population) will increase and not decrease the sum of human misery. "This argument appears to me to be a fallacious one, because it is founded on the assumption of some basic law which limits the possibilities of economic development to those which have been at the moment realized.

"This assumption appears to be unjustified. The students of agriculture paint for us a wholly different picture. Irrigation, control of erosion, the use of fertilizers, eradication of plant diseases, improvements in the type of animals and plants to be cultivated, and more efficient methods of food storage present enormous possibilities of increasing food production. The experts in FAO have set target goals which contemplate an increase of ninety per cent in the food-calorie yield of the less-developed areas by the year 1960, an increase which could not only provide for probable increases in the population, but also for a substantial improvement in standards of living.

"In many countries the development of mineral resources, of timber production, and of local industries could make possible the purchase of food from more purely agricultural areas. . . .

"The control of malaria in Sardina has made possible a plan now under way for settling a million Italians from the overcrowded mainland on that island. Up until now malaria has been the only barrier to fruitful agricultural development. . . .

"A most suggestive experience is that acquired in the building of the Pan-American Highway through Central America. Undernourished workers had produced most unsatisfactory results. Provision of an adequate diet for these workers more than doubled the day's work performance. In the opinion of the bureau in charge, the dietary deficiencies of the local population were not due to the lack of capacity of the area to produce food, but rather to the lack of transportation necessary to make food production profitable. Thus food makes possible the building of roads; and the building of roads makes possible the production of more food.

"The experience of the Pan-American Highway does, however, emphasize the vital inter-relationships between health and social problems. The public health program cannot be intelligently planned in a vacuum, but only as a vital part of a broader program of social reconstruction. In a particular area, higher crop yields, increased industrial developments, or improved transportation facilities may accomplish as much for health as more clinics and hospitals. . . .

"Improvement in health and prosperity may in itself tend to promote a better balance of population. In North-West Europe and in North America—the areas with highest economic status and lowest mortality—the annual excess of births over deaths is between four and six per one thousand population. This figure rises to fifteen for the near East and to twenty for Latin America. How far certain countries are rich because their population grows slowly and how far their populations grow slowly because they are prosperous is not easy to assess; but the general relation is clear.

"The building of a prosperous and a stable world depends on intimate collaboration between experts on public health, on agriculture, on engineering, on industry, on economics, and on sociology. It also demands a cooperation between governments and peoples, which is even more difficult to attain. The world cannot be saved by any one country alone; but only by the joint efforts of all our national sovereignties, from Afghanistan to Yugoslavia. Recognition of our common responsibility is the essential condition for survival. As Benjamin Franklin said in connection with Federal Union of the American colonies into a single state, 'we must indeed all hang together, or, most assuredly we shall all hang separately.' Yet the fact that the salvation of our separate national units is interdependent is not the real heart of the problem. Governments are, after all, only instruments for the welfare of human beings. The ultimate ideals of our policies must be based on a more fundamental factor, a deeper realization of the brotherhood of man—on the precious value of the individual human being. . . ."

The value of a man has been calculated in terms of the chemical elements in his body. Estimates of his worth in average productive capacity of goods and services are the basis for some of Dr. Winslow's calculations of economic gains from public health activity. Beyond this are the intangibles, the contributions to the human community which cannot be measured in specific terms, the contributions which make life more than existence. Community efforts for health—preventive medicine in the broadest concept—

bring in turn wealth in the broadest concept. It is highly fitting for the World Health Organization to take as its slogan for World Health Day, 1953, an old but axiomatic saw, "Health is Wealth."

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SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

THE PEDIATRICIAN'S RESPONSIBILITY WHEN HIS PATIENT IS ANESTHETIZED

By KENNETH D. ROGERS, M.D.,* AND SAMUEL M. WISHIK, M.D.
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Over the last decade or more, pediatricians have become increasingly aware that operative procedures can carry with them psychologic trauma for the child.[1] While it is not to be implied that every operation is a life-shaking experience upon which hinges the future happiness and security of the child, we do know that operations and their attendant events are well remembered by all of us, that they are found to be part of the "meaningful content" of psychiatric exploration, and that the onset of night terrors, disobedience, enuresis, excessive dependence reactions and similar disorders often follow operations. Unquestionably, the exact effect of these experiences on children varies both with the type of experience and with the basic security of the child. Although neurotic symptoms may have their origin in traumatic hospital experience, it is more likely that unfavorable reactions to hospitalization are caused by an activation or reinforcement of anxieties or neurotic trends already present.

Unfortunately, there has been a wide discrepancy between the acceptance of these ideas and the modification of present presurgical and surgical managment of the child to conform with them. The reasons are not hard to find, for the child patient has paid the price of specialization in medicine by having his pediatrician discover a condition, the surgeon elect to operate, the hospital nurse and physician manage the preoperating room experience, the anesthetist perform the potentially most upsetting procedure of the whole experience, and all these persons and others manage his postoperative hospital course.

Ideally, the parents would provide the continuity of security and consistency of management for which the situation calls, but since modern medical practice excludes them from many of the most vital parts of the experience and since they lack training to manage others, the parents cannot and are not permitted to provide the total answer. It is necessary, nonetheless, that someone provide the needed consistency of management of the child and the most logical person for this is his pediatrician. This does not mean that the pediatrician himself must perform all of the services, but it does mean that he must accept the responsibility for seeing that the management of his "whole" patient is optimally carried out.

One key part of the operative experience is that concerned with anesthesia. Because discussion of it has not appeared in American pediatric journals of the last few years, it

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was thought valuable to abstract some of the excellent contributions found in the literature of anesthesiology so that the pediatrician might increase his acquaintance with a subject which is of such importance to his patients.

The problem of anesthetic administration to the child can be divided into four parts: (1) the psychologic preparation of the child; (2) the pharmacologic preparation of the child; (3) the actual technic of anesthesia administration; and (4) handling during the recovery period.

The essence of psychologic preparation is to enable the child to anticipate the hospital and anesthetic situations so that their "unknown" and "sudden" components are eliminated. The questions which the pediatrician should explore are: who are the persons who will prepare the child, and what are the technics for doing so? For the child old enough to understand language, an honest explanation and description of both operation and hospital experience are necessary. The complexity of the description is, of course, varied with the ability of the child to comprehend. Children between one and five probably constitute the most difficult age group to handle since at these ages there is full awareness of all the emotionally upsetting aspects of the experience but limited capacity to understand and accept them. Critical stages of the psychosexual development of the child which occur during this time complicate the picture further.

Often the pediatrician has assumed that the parents will prepare the child, but quite often parents are unaware of the importance of preparation or their own anxiety and lack of information incapacitate them for this task. In other situations the pediatrician has utilized the hospital psychiatrist or psychiatric social worker for this, but, if for no other reason than the unavailability of such specialized personnel in most hospitals, this solution is not possible for general application. It has been the anesthetist who has been ultimately confronted with the problem of managing a poorly prepared, frightened, and uncooperative child and it has been the anesthetist, therefore, who has worked out technics to solve this problem.

These technics have varied from a few advance instructions to the child on the proper way in which to breathe to the more extensive programs of psychologic preparation such as the one which Jackson describes.[2] "The preanesthetic conversation between the child and the anesthetist took place in the early evening of the preoperative day. At that time the anesthetist was dressed in ordinary street clothes. If the mother was with the child, she was included in the interview to the extent of supplying information not obtainable from the patient. Attention was always directed toward the child, however, and he was encouraged to speak for himself. The following outline presents the general plan and purpose of the interview:

"1. Learn whether the child has had previous anesthesia experience and determine its present influence.

"2. Learn what preparation he has had at home—planned or accidental, positive or negative.

"3. Explain that he is to be asleep and will feel no pain during the entire procedure except for a sore throat (in the case of tonsillectomy) after it is over.

"4. Let him handle the mask and explain that breathing the medicine will make him fall asleep.

"5. Describe simply but realistically the dizzy, queer or sinking feeling that he may have as he goes to sleep.

"6. Describe the operating suite and dress of personnel including the anesthetist.

"7. Most important of all, do and say whatever is necessary to get him to accept the anesthetist as a person whom he will be willing to trust."

Jackson felt, in addition, that the general atmosphere of the pediatric ward in which the patients were cared for was important. "Any child who enters this department is made to feel by doctors, nurses, and attendants, that he is a welcome guest. His happiness is as much their concern as is his physical welfare. . . . Except in such an atmosphere, the previously described preparation by the anesthetist would have been much less effective."

The pharmacologic preparation of the child has several purposes: to allay apprehension, to prevent excessive secretions in the respiratory tract, and to reduce the amount of volatile anesthetic needed. Whereas some anesthetists are of the opinion that psychologic preparation alone is adequate to insure a psychically atraumatic induction, other anesthetists rely on varying depths of preanesthetic sedation to allay apprehension. These range from a light dose of barbiturate which is intended to "quiet the child" to deep basal anesthesia with rectal pentothal or avertin. Most anesthetists include atropine or scopalamine in the preanesthesia and some use combinations of morphine or demerol with barbiturates.[3] Consultation between the pediatrician and the anesthetist helps in the selection of an anesthetic agent appropriate to the child's past medical history and the pediatrician's evaluation of his personality.

Artusio and Trousdell[4] made a comparative study of one hundred tonsillectomies performed on children and pointed out the effects of preinduction sedation on memory of and emotional reactions to the hospital experience. Fifty of the children received rectal pentothal and 50 received morphine and atropine as premedication. The group which was to receive the rectal pentothal was admitted the night before the operation. The anesthetist visited at that time in order to evaluate each child emotionally and to become acquainted with him. The following morning, the anesthetist gave the child rectal pentothal in his own bed. "During the next few minutes, the anesthesiologist talked quietly to the child, observing him as he became drowsy and fell into a light sleep. When the child did not respond to his name, an additional five minutes was allowed before he was moved. . . . During the trip from the ward to the operating room, the anesthesiologist stayed at the head of the bed to observe color, respiration, and any untoward reaction which might occur."

In the group which was to receive morphine and atropine, "The children were admitted to the hospital on the morning of the operation. The anesthesiologist visited the child to make his acquaintance and to evaluate his emotional status. The child was given morphine and atropine . . . pre-operatively and was brought to the operating room fifteen minutes before the beginning of the operation. The anesthesiologist attempted to make the child feel at ease. Story books and toys were present for the child to play with before the induction was begun."

The authors found that the group receiving preanesthesia with rectal pentothal had fewer unpleasant recollections of the hospital experience and postoperatively had fewer emotional disturbances such as nightmares, anorexia, irritability and enuresis. They concluded that the only real disadvantage of the rectal pentothal premedication over the morphine-atropine was the necessity for the anesthesiologist to stay with the child from the beginning of the rectal instillation to the conclusion of the anesthesia—a factor which would render it impracticable in some institutions.

The actual anesthetic induction in the operating room—the event towards which all

preparation is directed—draws on the full science and skill of the anesthetist. Because of ether's peculiar odor, respiratory tract irritation and the sense of suffocation associated with its use, some anesthetists elect to use vinethene or nitrous oxide for the induction. Many clever technics for reducing terror at this stage have been devised. Some anesthetists use the technic of story telling or "make believe," one reports that use of a whistle that fits into the exhalation side of a gas anesthetic machine encourages the young patient to blow, thereby increases depth of respiration and induces anesthesia rapidly, and an Irish dentist uses a transparent plastic mask to lull children's fears. It is common for the anesthetist to elicit the child's cooperation by allowing him to hold the mask.

Thomas,[5] of the Royal Berkshire Hospital in Reading, England, reports his method. "If the child is awake, I explain quietly that I want his help in making him go to sleep, and hold the mask two inches or so from his face, chatting to him, and telling him that he will smell a funny smell which will make him sleep. At this stage I run eight liters of nitrous oxide and two liters of oxygen through. This is rather arbitrary as it is equally possible to use pure nitrous oxide. The essential is a rapid large flow of gas. The child is invited to close his eyes 'for he cannot go to sleep with his eyes open.' *The mask is then held half an inch from the face,* and, if all goes well, deepening respiration shows that anesthesia is being established within about two minutes. The mask is then lightly rested on the face. . . .

"Variations of the technic can be introduced according to the circumstances. For instance, a non-cooperative child can sometimes be persuaded to curl up under the blanket, the end of the tube, without a mask, being inserted under the blanket and pure oxygen being run in to begin with and then increasing nitrous oxide until respiratory deepening shows the onset of anesthesia."

Jackson[2] says of the induction of the anesthetic: "The child who has appeared fearful during the pre-operative visit must be reassured from the beginning of induction and constantly until all possibility of consciousness and subjective sensation is past. With experience, the anesthetist can discern from the child's breathing, the tension in his face and hands, and many other little signs, what he needs to prevent panic from developing. The child who is obviously and truly unafraid needs less conversation and often seems to be better without it.

"It requires some skill and understanding to discern when the unresponsive child needs reassurance and positive expressions of understanding. The child may seem indifferent, although we know that this is impossible, or he may even seem to be accepting, until he begins to feel the effects of the anesthesia. Even then he may give little evidence of apprehension; he may open his eyes and look at the anesthetist, hold his breath a few seconds, tense his muscles or move the mask. If the feeling between the child and the anesthetist has been even fair the night before, this resistance is always mild, in fact it has a tentative quality about it. In almost every case, the child will relax and cooperate when the anesthetist's voice is heard. It does not seem to matter much what is said as long as the tone is understanding and comforting."

Deming,[6] in speaking of the same subject, summarizes her article: "In general, it may be stated that the less traumatic the induction of anesthesia is for the child, the greater is the anesthesiologist's contribution to the general well being of the pediatric surgical patient and the better will be his rapport with the child's parents, his surgeons, and his pediatrician."

The recovery stage from anesthesia may be arbitrarily divided into two periods. During

the first, the child recovers essential reflexes (gag, swallow, corneal) and vomits if such is going to be the case. He is usually semiconscious at this time and often wild and uncooperative. In many hospitals the practice is to keep the child in a "recovery room" adjacent to the operating suite during this time and to have a nurse or anesthetist in attendance. In the case of procedures such as tonsillectomy, one nurse can take good care of several patients simultaneously. The advantages of being near the operating room with its facilities and personnel as well as the constant attendance of a nurse are obvious. The second period is considered to occur after the child has "responded" to the extent that he is able to manage his own respiratory secretions and vomitus if such should occur. His awareness grows progressively during this time and the child becomes increasingly conscious of the strangeness of his surroundings, his pain, etc. It is probable that the presence of the parents will do much to alleviate the terror and discomfort at this time and effort should be made to have them at the bedside when the child awakens.

Thus, at different phases of anesthetic administration there are psychologic factors which, if considered, could probably render the child's hospital experience less unpleasant. Although the pediatrician has ever increasing duties and responsibilities which fill his time, it still behooves him as the child's doctor—the member of the medical profession with concern for the "whole child"—to see that the child receives adequate psychologic preparation for his operative experience, that the anesthetic experience is minimally traumatic, and that the postoperative hospital experience is as pleasant as possible. If personnel are not trained or available to insure all these things, the pediatrician must be ready to supervise these functions himself or must, at least, investigate the situation, become informed on what really goes on, and work for improvement.

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SPECIAL ARTICLE

EARLY HISTORY OF FLUID REPLACEMENT THERAPY

By JAMES L. GAMBLE, M.D.
Boston

THE long story of the development of fluid replacement therapy has an abrupt and clearcut beginning which we find recorded in a brief letter from an English physician to the *Lancet*[1]:

EXPERIMENTS ON THE BLOOD IN CHOLERA.

To the Editor of THE LANCET.

SIR,—Having been enabled to complete the experimental inquiries on which I have some time back been engaged in Newcastle upon-Tyne, I beg you will have the kindness to give insertion to the annexed outlines of the results I have obtained:—

1. The blood drawn in the worst cases of the cholera, is unchanged in its anatomical or globular structure.

2. It has *lost a large proportion of its water*, 1000 parts of cholera serum having but the average of 860 *parts of water*.

3. *It has lost also a great proportion of its* NEUTRAL *saline ingredients.*

4. *Of the free alkali contained in healthy serum, not a particle is present in some cholera cases, and barely a trace in others.**

5. Urea exists in the cases where suppression of urine has been a marked symptom.

6. *All the salts deficient in the blood, especially the carbonate of soda, are present in large quantities in the peculiar white ejected matters.**

I am, Sir,
Your obedient servant,
W. B. O'SHAUGHNESSY, M.D.
London, 29 December, 1831.

FIG. 1

Annual Robert J. Terry Lecture, Washington University Medical School, St. Louis, April 9, 1952.
(Received for publication Feb. 25, 1953.)

Dr. O'Shaughnessy promised to submit a "detailed report in which the mode of analysis and so forth will be minutely described." This he presently did. Meanwhile a general practitioner in the small city of Leith in Scotland who read his *Lancet* faithfully saw at once the therapeutic implications of Dr. O'Shaughnessy's observations. The name of this enterprising doctor was Thomas Latta, and to him belongs the credit of being the first to employ intravenous injection of a solution of sodium salts to replace losses incurred by diarrhoea. His first patient was an old lady severely sick with the cholera. The dramatic outcome of this historic adventure in therapy is recorded in a beautifully written report which Dr. Latta sent to the *Lancet*,[2] May 23, 1832. He tells us that "she had apparently reached the last moments of her earthly existence and now nothing could injure her—indeed so entirely was she reduced that I feared that I should be unable to get my apparatus ready ere she expired. Having inserted a tube into the basilic vein, cautiously —anxiously I watched the effects: ounce after ounce was injected but no visible change was produced. Still persevering, I thought she began to breathe less laboriously. Soon the sharpened features, and sunken eyes and fallen jaw pale and cold, bearing the manifest impress of death's signal began to glow with returning animation, the pulse which had long ceased returned to the wrist, at first small and quick, by degrees it became more distinct, fuller, slower, firmer and in the short space of half an hour when six pints had been injected she was free from all uneasiness, actually became jocular, and fancied that all she needed was a little sleep; her extremities were warm and every feature bore the aspect of comfort and health."

Six hours later Dr. Latta's first patient died. But this valiant physician was not discouraged. He thereupon realized that repeated injections may be required. During the epidemic he treated 16 patients who were near the edge of existence and rescued 8 of them. A few other physicians ventured to try this new treatment and sent case reports to the *Lancet* describing "miraculous" recoveries.

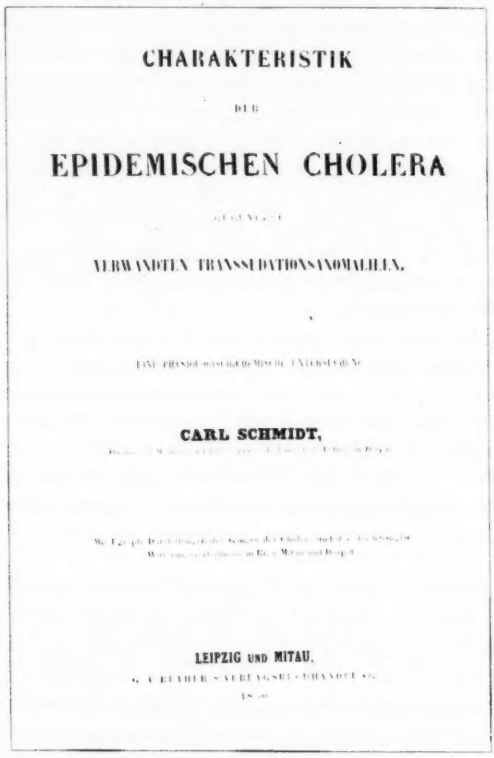
The solution which Dr. Latta and his followers used contained about 0.4% sodium chloride and 0.3% sodium bicarbonate, so that it was an approximately isotonic solution. They found that in order to save their patients several injections of 2 to 3 liters might be required.

They thus inadvertently covered the all-important requirement for adequate repair of dehydration. They were not aware of the relation of water loss to circulatory failure. Their concern was to supply enough of the curative sodium salts, but their bedside observations guided them correctly. So that in the year 1832 both the rationale and the effectiveness of fluid replacement therapy were roughly but adequately demonstrated.

But the medical community was not persuaded to accept so bold a therapeutic procedure. It was used only in the advanced stage of the disease and many patients did not survive. Opposition was voiced vigorously by the conservatives. Physicians were amused that a lack of alkali in the blood should be regarded as the cause of cholera; the concept of supportive therapy seems to have been entirely lacking. The *Lancet* gave valiant editorial support to the new treatment but the epidemic came to an end before acceptance could be established and O'Shaughnessy's large gift to medical science was soon forgotten. Sixty years later the efficacy of parenteral fluid therapy in the treatment of cholera was rediscovered by Cantani[3] during an epidemic in Naples. His findings in the blood were the same as O'Shaughnessy's and reports from clinicians were as lyrical as those of Dr. Latta and his followers. But again fluid therapy did not receive general acceptance. German physicians found it ineffective for the now evident reason that the quantity of

fluid provided was inadequate. Fluid therapy in cholera was eventually established in the early part of this century by the work of English physicians in India and of Sellards in the Philippines.*

Although lack of appreciation of the urgency of the requirement for volume restoration in order to rescue severely dehydrated patients from circulatory failure was the cause of the long lag in acceptance of replacement therapy, repair of structure is also an obvious assignment in the treatment of body fluid disturbances and must rest on knowledge of distortions caused by disease. O'Shaughnessy's crude observations on the sodium salts in the blood pointed out this approach, and today we continue to follow



CHARAKTERISTIK

DER

EPIDEMISCHEN CHOLERA

VERWANDTEN TRANSSUDATIONSANOMALIEEN.

CARL SCHMIDT,

LEIPZIG UND MITAU.

FIG. 2

this path. So it is appropriate to recall the work of a great chemical anatomist of the last century, Carl Schmidt, who was a pupil of Liebig and became professor of physiologic chemistry at the University of Dorpat in Esthonia. With his colleague, Bidder, he measured in animals the daily volume and described the chemical structure of each of the digestive secretions in complete detail.[4] During an epidemic of cholera in Dorpat, Schmidt

* The cholera chapter in the history of fluid therapy has been recorded, with additional interesting citations from *Lancet,* by Dr. Ebsen Kirk in his excellent monograph on acidosis published as supplement 183 to *Acta Medica Scandinavica,* 1946, and is also related by Dr. Carl A. Moyer in his recent book *Fluid Balance* (Chicago, The Year Book Publishers, 1952).

carried out remarkably complete analyses of blood from healthy individuals and from cholera patients. He also analyzed vomitus and stools from these patients. His measurements are recorded in a small book published in the year 1850.[5] As indicated on the title page (Fig. 2) he regarded the digestive secretions as transudates which implies his awareness of the hazard to the chemical structure of the blood from wastage of these secretions by vomiting and diarrhoea. He did a thorough job on the blood, analyzing separately whole blood, the blood cells, the plasma which he called intercellular fluid, and blood serum. Using the ponderous methods of his time this took a lot of blood. About 200 cc. was required. This he tells us was obtained by "eine augenblickliche venesection." This quaint little statement gives us a vivid picture of collecting a blood sample in those times.

His measurements for blood serum from one of his healthy subjects are shown in table 1. The weights per liter of the individual inorganic components, except for calcium and magnesium which were measured together, are recorded in the left hand column. This was 30 years before Arrhenius demonstrated the dissociation of salts in solution into their component ions. So it was necessary to stick the anions and cations together again in order to provide a suitable assortment of salts. His choice of salts for blood serum is shown on the other side of the table, where it is also recorded that quite a bit of sodium was left over. This sodium surplus is just about right for covering the base equivalence of his measurement of albumin together with the values which we now accept as usual for organic acids and bicarbonate ion which he did not measure.

The milliequivalent per liter values for the individual ions in blood serum which we regard as average normal are given in the first column of table 2. In the next column Schmidt's measurements are recorded in this term. The accepted value for organic acids, which he did not measure, is used in this column and the value for HCO_3 was obtained by subtracting the sum of the other anions from the total cation value. The close agreement of Schmidt's measurements with the standard values of nowadays is impressive evidence of the reliability of the methods of those times and of his skill in using them. Measure-

TABLE 1

1000 Gr. Serum

Wasser				917,15
bei 120° nicht flüchtige Stoffe				82,85
Albumin etc.				74,43
unorganische Bestandtheile				8,42
Chlor	3,659	=	schwefels. Kali	0,218
Schwefelsäure	0,100	=	Chlorkalium	0,448
Phosphorsäure	0,238	=	Chlornatrium	5,677
Kalium	0,333	=	phosphors. Natron	0,444
Natrium	3,183	=	Natron	0,077
phosphors. Kalk —Magnesia	0,552	=	phosphors. Kalk —Magnesia	0,552
Sauerstoff	0,351			
Summe der unorganischen Bestandtheile				8,416

Dichtigkeit = 1,0261.

TABLE 2

Blood Serum		Average Normal	Carl Schmidt, 1850	
			Normal	Cholera
Cations, mEq./l.	Na	142	139	117
	K	5	8	11
	Ca, Mg	8	9	4
		155	156	132
Anions, mEq./l.	HCO_3	27	22†	5†
	Cl	103	104	87
	HPO_4	2	4	5
	SO_4	1	2	6
	Org. AC	6	6*	6*
	Protein	16	18	23
		155	156	132

* Not measured.

† Total cation—other anions.

ments from one of his cholera patients are given in the last column. The loss of water from the serum and the relatively larger loss of electrolytes caused by the severe diarrhoea of cholera are shown by the increased albumin content along with reduction of total base. The severe acidosis of cholera, which Sellards[6] demonstrated in 1911 by measuring the plasma dicarbonate directly in the Van Slyke burette, is clearly defined by the large reduction of the value for HCO_3 derived from Schmidt's other measurements. His analyses of whole blood and of blood cells provide detailed description of other changes caused by dehydration.

So that, using the milliequivalent as an archeologic tool, we find that the basis for reparative therapy in diarrhoeal dehydration, which we are accustomed to regard as knowledge gained in our time, was completely and accurately built by Carl Schmidt 100 years ago, and we are astonished that clinical application of this fine work was not undertaken. As a chemical anatomist Schmidt was evidently a perfectionist. Perhaps he felt that direct repair of the many defects he found in the blood would be quite impossible. What this moment of opportunity lacked was a physician of Dr. Latta's courage and naïveté. During a devastating epidemic of cholera which occurred in Denmark a few years after the publication of Schmidt's studies no defense of the body fluids was attempted.

During the great period of German pediatrics from about 1890 to World War I, diarrhoeal disease was intensively studied. Analysis of the blood of infants was not practicable because of the exorbitant quantity required by the methods of those days. A large and important addition to chemical anatomy was however made by the heroic procedure of analyzing the whole bodies of infants. Needless to say these studies were not numerous. Indeed, our knowledge of normal values rests largely on the famous five infants dying at birth of obstetric trauma analyzed by Camerer and Soldner.[7] Analyses of various tissues taken from infants dying of diarrhoeal disease were carried out by several investigators, and in a few instances whole body analysis was undertaken. The

outcome of this work was a polemic as to whether the large losses of water and substances in diarrhoea altered the normal composition of the body. The view that the relative quantities of the components were fairly closely preserved eventually prevailed and the situation which we now call dehydration, because the word points to the immediately dangerous event, was regarded as a state of rapid emaciation which was described by the dreadful word "decomposition." Had they chosen the word "desiccation" instead, they would doubtless have found the path to fluid therapy. They were further misled by Finklestein's designation of severe diarrhoea as "intestinal intoxication." The notion of absorption of some poisonous substance from the disordered intestinal tract came from the symptoms of disturbance of the nervous system, such as muscular twitching, alternating irritability and drowsiness, and eventually coma, which develop in the last stage of diarrhoeal disease. These symptoms used to be regarded as evidence of so-called toxemic states. They closely resemble those of uremia for instance. Now that we know that they result from failure of the functions of extracellular fluid and disappear directly dehydration is repaired and renal function restored by replacement therapy, we no longer need the concept implied by that glib word toxemia. Nor by the same token is it any longer required in Bright's disease.

Again we note the missing concept which makes the plot of this story: failure to recognize the importance of the physiologic dimension, volume. The requirement for constancy of the internal environment had been pointed out by Claude Bernard but it was not until many years afterward that clinicians learned from Lawrence Henderson the importance of this great concept. It must also be remembered that in those times the structure of the internal environment of infants could not be directly examined and was incorrectly inferred to be intact on the basis of tissue analyses.

So parenteral therapy had to wait for the development in this country of micromethods of measurement which permitted description in the blood of infants suffering from diarrhoeal disease of the changes which Carl Schmidt found in the blood of cholera patients 100 years ago. The urgent importance of restoration of the volume of extracellular fluid was not immediately recognized.[8] The discovery of the acidosis of severe diarrhoea by Howland and Marriott and independently by Schloss and Stetson[9] was an exciting event and focussed attention on repair of this structural defect by intravenous administration of sodium bicarbonate. Volume restoration was not entirely neglected. Salt solution was also given subcutaneously but not to an adequate extent. Fortunately there was a Dr. Latta at hand. Dr. Howland's perennial resident, Kenneth Blackfan, watched over his patients with a devoted solicitude and decided that they needed lots more salt solution. To gain this end he gave salt solution by intraperitoneal infusion.[10] His results were completely convincing. But again as in Dr. Latta's time there was outcry. The surgeons were appalled that a pediatrician should have the temerity to "enter" the abdomen. Then came the classical work of Marriott and Utheim[11] which demonstrated the disastrous effect of dehydration on the circulation of the blood and Schloss' fine work[12] describing the resulting impairment of renal function which explains development of structural defects in the body fluids. The understanding of events in dehydration which these studies provided made clear the urgency of the requirement for replacement of fluid losses.

So at long last in the early 1920's the rationale of a procedure which seemed obvious to a bedside doctor 120 years ago was established on an irreproachably scientific basis, and the life-saving effectiveness of sustaining extracellular fluid was dramatically demonstrated by reduction of the mortality of severe diarrhoeal disease from somewhere

near 90% to about 10 or 12%. Until recently we were content with so splendid an achievement against this ancient scourge of infants although we knew that along with sodium there is a large loss of potassium in diarrhoeal stools, which presumably measures a deficit of intracellular fluid. We lamented that nothing could be done about this because of the hazard of harm to the heart from parenteral administration of an appreciable quantity of potassium. So we had to wait for the daring Daniel Darrow, who isn't afraid of a postulation, to show us that, if reasonable precautions are observed, potassium can be safely used in a repair solution and is entitled to a place in fluid therapy.[13]

The title of this lecture permits me to avoid attempting to appraise the current commotion about the position of potassium in the pathogenesis and therapy of various conditions of disease. So we will go back again to the last century and consider an almost forgotten observation published in the year 1873 by the German physiologist Bunge which has an obvious relevance to the use of potassium and sodium in fluid therapy. According to Bunge, a large addition of potassium to intake will cause a loss of sodium from the body which will be approximately equivalent to the extent of potassium retention. And, the other way round, a sodium gain from increase of intake will be accompanied by a loss of potassium. If this inverse relationship holds under varying circumstances, the desirability of a balanced provision of sodium and potassium in fluid therapy is clearly indicated.

Bunge was, at the time that he reported this finding, an assistant in the chemistry laboratory of the University of Dorpat, apparently one of Carl Schmidt's younger men. He eventually became professor of physiologic chemistry at Basle and wrote a textbook of physiologic and pathologic chemistry. In 1902, the fourth German edition was translated into English by Professor Starling's wife and edited by Starling who has this to say of him in his introduction: "Professor Bunge's lectures on physiological chemistry have had a great influence on physiological thought both here and abroad. These lectures have also the merit of being written by a man who was a philosopher, mathematician and chemist before he was a physiologist and who, being in a position to grasp the general bearings of this subject, has succeeded in making the dry bones of physiological chemistry interesting even to the beginner." Professor Starling was quite right. Bunge wrote very entertainingly. Thanks to the English edition, I have read quite a lot of his textbook with much enjoyment. I cannot refrain from citing a few passages from his chapter on the Inorganic Food Stuffs which relate the genesis of his curiosity about sodium and potassium.[14]

"There is only one inorganic salt about which I must add a few words, because it holds a rather exceptional position—common salt.

"It is a very remarkable fact that of all the inorganic salts in our bodies we only take one with our organic food-stuffs, and that is common salt. We obtain enough of all the other salts from the amount contained in our food, and we never think of providing ourselves with them separately. Common salt forms the only exception, which is the more remarkable as our diet is by no means deficient in it. All vegetable and animal food contains considerable quantities of chlorin and sodium. Why do these quantities not suffice, and why do we add common salt?

"In the earlier experiments made to decide this point, one fact was quite overlooked, which appears to me likely to lead to a correct solution of the difficulty. I mean the fact that the desire for salt in the food is only observed in the case of herbivora, and never in the case of carnivora. Our carnivorous domestic animals, the dog and the cat, prefer unsalted to salted food, and show great dislike to very salty food, while the domesticated

herbivora are well known to be very found of salt. The same thing has been observed in wild animals. It is a known fact that wild ruminants and hoofed animals seek out salt-rocks and pools, and places where salt effloresces, to lick the salt, and that hunters watch for them at such places, or expose salt as a bait. This has been noticed by numerous travellers to hold good for herbivora of all countries and climates, but it has never been observed in the case of beasts of prey.

"The difference is the more striking as the amount of salt which herbivorous animals take in with their food is, compared with the weight of the body, generally not much less than that consumed by carnivorous animals. On the other hand there is a considerable difference in another constituent of the ash of their food, in the potassium. Herbivorous animals take at least three or four times as much of salts of potassium as the carnivora. This fact leads me to imagine that the abundance of potassium in vegetable food is the cause of the need for salt in the herbivora.

"A man who lives chiefly on potatoes takes, in the course of the day, up to 40 gms. of potassium. This shows why potatoes are so unpalatable without salt. Like potatoes, all the other important vegetable articles of diet, the cereals and legumes, are very rich in potassium, and this explains the fact that country people, living mainly on a vegetable diet, use more salt than the inhabitants of towns, who eat a great deal of animal food. It has been statistically shown in France that people living in the country eat three times as much salt per head as those in towns.

"We may now ask what the people do who take no vegetable food at all. There are whole tribes of hunters, fishermen, and other nomads, who live entirely on animal food. We might expect that these people would, like the carnivorous animals, have a disinclination for salt. This is in fact the case. In order to ascertain this, I have gone through a very large number of works of travel, and have obtained a great deal of information from travellers, either personally or by letter. From all this it appears to be a universal rule that in all times and in all lands those people who live entirely upon animal food either have never heard of salt, or, if they possess it, avoid it; whereas the people whose staple food is vegetable have the greatest desire for it, and regard it as an indispensable article of diet.

"This difference was manifested as far back as the ancient Greek and Roman times, when the sacrificial animals were always offered to the gods without salt, but the fruits of the earth with salt. The Mosaic law expressly commanded the Jews to present their vegetable offerings accompanied by salt to their Deity."

Here is a passage in which we find recognition of the extracellular position of sodium. "The beast of prey, which devours every part of an animal, obtains potassium and sodium in almost equal quantity. On the other hand, four equivalents of potassium are present for every equivalent of sodium in the bloodless meat of slaughtered animals. It is therefore noteworthy that the people who live on an animal diet without salt, carefully avoid loss of blood when they slaughter the animals. This was told me by four different naturalists, who have lived among flesh-eaters in various parts of northern Russia and Siberia. The Samoyedes, when dining off reindeer-flesh, dip every mouthful in blood before eating it. The Esquimaux, in Greenland, are said to plug the wound as soon as they have killed a seal. Among the Masai, a tribe of eastern equatorial Africa, who during their period as warriors from seventeen to twenty-four years of age, live exclusively on an animal diet without salt, blood is regarded as the choicest and most desirable of all articles of food."

These considerations led Bunge to set up a biologic ratio for the intake of sodium and

potassium based on analyses of the milk and of the bodies of sucklings of various animal species. He then carried out a few experiments on himself to find out what happens if this ratio is extensively disobeyed.[15]

The outcome of an experiment in which he ingested 29 gm. of potassium phosphate on the fifth day of a period of study on a food intake of constant composition is shown in table 3. His measurements of weights of the oxides have been converted to milliequivalents. Using the measurements of outgo in the urine on the fourth day as a basis, rough definition of change in balance can be derived. The data described a large retention of potassium and a closely equivalent loss of sodium from the body, and so they sustain Bunge's postulation of a reciprocal relation of potassium gain and sodium loss almost perfectly, much better, we may note, than this measurements of balance expressed as weights of the oxides.

TABLE 3

BUNGE'S POTASSIUM PHOSPHATE EXPERIMENT

29 gm. K_2HPO_4 added to intake on 5th day
=332 mEq. K

	K mEq.	Na mEq.	Cl mEq.
Urine 4th day	47	48	55
Urine 5th day	242	178	154
Increased outgo	+195	+130	+ 99
Addition to intake	332	0	0
Balance	+137	−130	− 99
3-day after period	− 82	+ 76	+ 86

(Ztschr. f. Biol. 9:104, 1873.)

In another experiment (table 4) in which the ingested salt was potassium citrate he again found an approximately equivalent retention of potassium and loss of sodium. Then on the ninth day of this period of study, sodium citrate was ingested. There was loss of potassium but to an extent which was far short of the large retention of sodium. Obviously however this experiment followed the potassium experiment much too closely and its evidence cannot be regarded as dependable.

Bunge was apparently content to rest his large thesis on these few experiments. His potassium experiments came out on the mark, but quite evidently we should have better definition of the effect of sodium salts than his citrate experiment provides.

In a recent paper by Leaf, Couter and Newburgh[16] there are excellent data on the effects of large intakes of sodium chloride and of sodium citrate on potassium balance (table 5). Two of the subjects receiving sodium chloride lost small amounts of potassium. Another subject gained potassium. In the sodium citrate experiments there were sizeable losses of potassium which, however, were only about one-third of the equivalence of the large retentions of sodium. According to the outcome of the sodium chloride experiments we need not worry about a Bunge effect when we use salt solution in fluid therapy.

However, in studies on the life raft ration carried out during the war years,* Bunge

* These studies carried out for CMR under the direction of Dr. Allan M. Butler have not been published *in extenso*. Charts 1 and 2 are from lectures by the author.[17]

TABLE 4

BUNGE'S CITRATE EXPERIMENTS

332 mEq. K added to intake as K-citrate on 5th day

	K mEq.	Na mEq.	Cl mEq.
Urine, 4th day	37	72	93
Urine, 5th day	258	188	197
Increased outgo	+221	+116	+104
Addition to intake	332	0	0
Balance	+111	−116	−104

332 mEq. Na added to intake as Na citrate on 9th day

	K mEq.	Na mEq.	Cl mEq.
Urine, 8th day	66	26	34
Urine 9th day	82	255	29
Increased outgo	+ 16	+229	− 5
Addition to intake	0	332	0
Balance	− 16	+103	+ 5

effect under a sodium chloride load was encountered in the state of fasting following a period of thirsting.

The speckled columns in chart 1 record the average daily deficits for the individual electrolytes over a four day period of thirsting and the stripped columns the values found in a subsequent period during which the subject drank 500 cc. of sea water daily. The relatively large intake of sodium and chloride which sea water provides caused extensive reduction of the deficit found for sodium (and chloride) during the period of thirsting but there was a large increase of the loss of potassium.

TABLE 5

EFFECTS OF LARGE LOADS OF NaCl AND OF Na-CITRATE

478 mEq. Na daily added to low sodium diet
(NaCl, 28 gm. Na citrate, 47 gm.)

Subject	Balances for 3-day Periods			
	NaCl Load		Na-Citrate Load	
	Na mEq.	K mEq.	Na mEq.	K mEq.
E. W.	+553	− 9	+436	−108
M. L.	+355	+46	+236	− 76
W. C.	+759	−60	+303	−133

Data from Leaf, Couter and Newburgh.[18]

In other experiments in which 100 gm. of carbohydrate daily was given with an ample water intake, the Bunge effect was found again when an intake of sodium or of potassium was provided. In chart 2 the daily measurements of balance are recorded additively over six day periods. The progress of loss of sodium and of potassium when no salt was given is recorded in the first section of the chart and the effect of an intake of 4.5 gm. of sodium chloride is shown in the next section. There was almost complete conservation of sodium accompanied by a large extension of potassium deficit. It may be noted that the sodium intake was small; provided parenterally it would be contained in a half liter of physiologic salt solution. In the last section of the chart the inverse effect of an intake of potassium chloride is shown.

Parenteral therapy is undertaken in situations which extensively, often completely, interfere with oral intake of water and food. The evidence of these experiments, carried out on healthy subjects in states of fasting and thirsting and of fasting with water, is therefore relevant and apparently indicates the desirability of a balanced provision of sodium and potassium in fluid replacement therapy.

By way of support for this inference the data recorded in chart 3 are presented.[17] They are from an admirable study carried out by Dr. William Wallace in which it was undertaken to describe the progress of replacement of sodium and potassium deficits

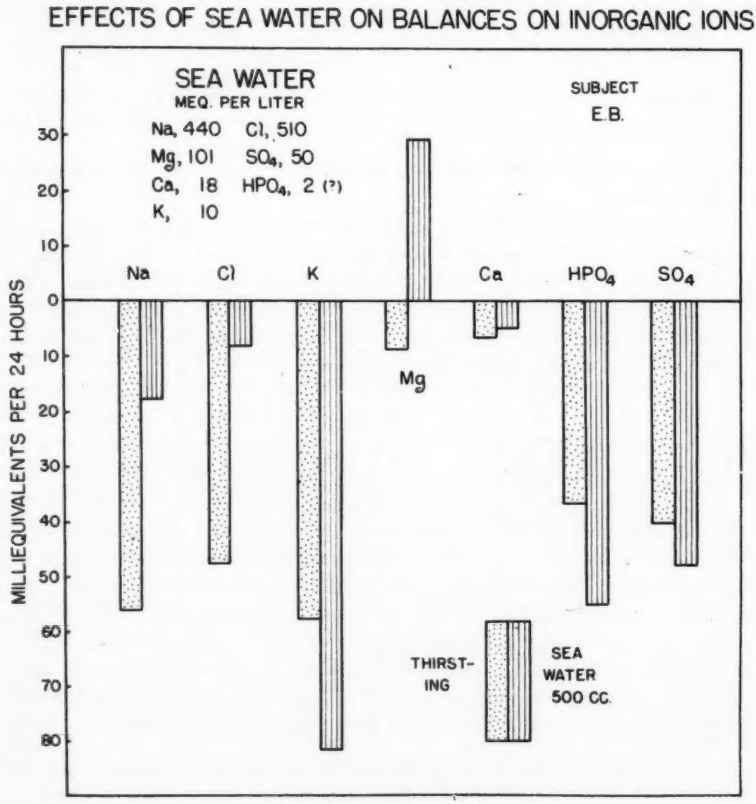


CHART 1

over a 14 day period of treatment of severe diarrheal dehydration. The daily values found for balance are recorded additively. The infant was given fluids parenterally the first two days and then orally for two days. The fluids used were glucose solution and Darrow's sodium-potassium-lactate solution. In addition, because of acidosis and distressing hyperpnoea, a large infusion of sodium bicarbonate was given at the outset of treatment so that the infant received on the first day a large excess of sodium over potassium. There was an immediate huge retention of sodium but no gain of potassium over the first four days. This can be explained as Bunge effect from the large retention of sodium.

Over the next four days small feedings of fat-free milk were given with a good-sized

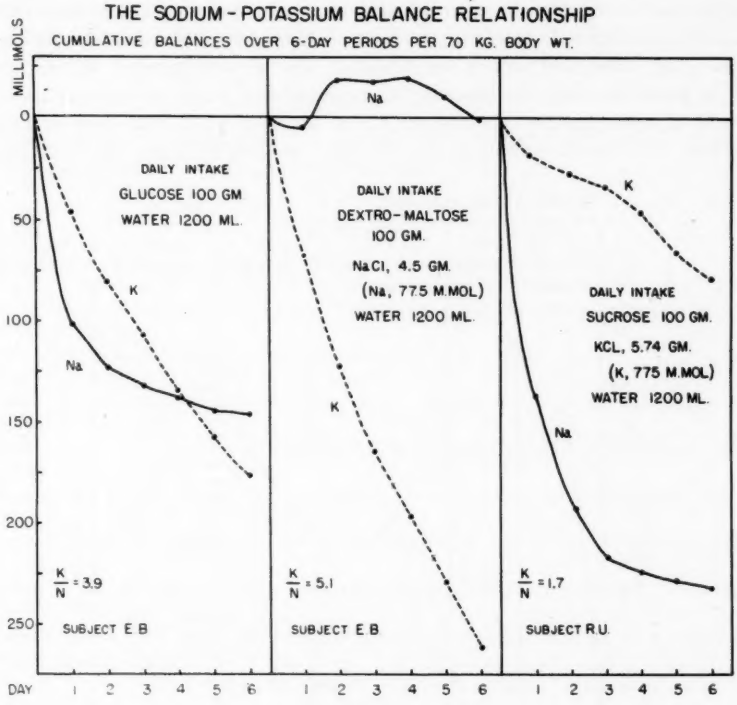


CHART 2

supplement of potassium. There was then rapid gain of potassium and along with it an approximately equivalent removal of sodium. Here we can quite clearly recognize Bunge effect. Over the subsequent periods of milk feeding without added potassium, sodium and potassium gains go along quite amiably together. The chart suggests that a properly balanced intake of sodium and potassium would have produced a parallel replenishment of both deficits. This is not to say that for the sake of a better looking chart treatment of the initial acidosis with sodium bicarbonate should have been omitted. The chart is presented simply to illustrate the operation of Bunge effect in the course of treatment of diarrhoeal dehydration and the desirability of providing potassium along with sodium within the limits of safety and practicability.

This old observation of Bunge's has been dealt with at this length because it deserves more recognition than it has received and more accurate definition. Evidently, according to Bunge's own experiments and those of Leaf, Couter and Newburgh, the effect of a sodium load is not unconditional. Attempt to explain Bunge effect should be a rewarding adventure in the direction of learning more about electrolyte relationships.

Bunge himself had not the slightest difficulty in explaining the outcome of his experiments. In those pre-Arrhenius times the body fluids contained salts, not ions, and chemical events had to be explained on the basis of their interactions. Bunge's account of what went on in his potassium salt experiment is an interesting example of a biochemist's imagination on this old premise.

He tells us that when "a salt of potassium, such as potassium carbonate, meets with common salt or chloride of sodium in solution a partial exchange takes place; chlorid of potassium and carbonate of sodium are formed. Now chlorid of sodium is well known to be the chief constituent among the inorganic salts of blood-plasma. When, therefore, salts of potassium reach the blood by the absorption of food, an exchange takes place. Chlorid of potassium and the sodium salt of the acid which was combined with the potassium are formed. Instead of the chlorid of sodium, therefore, the blood now con-

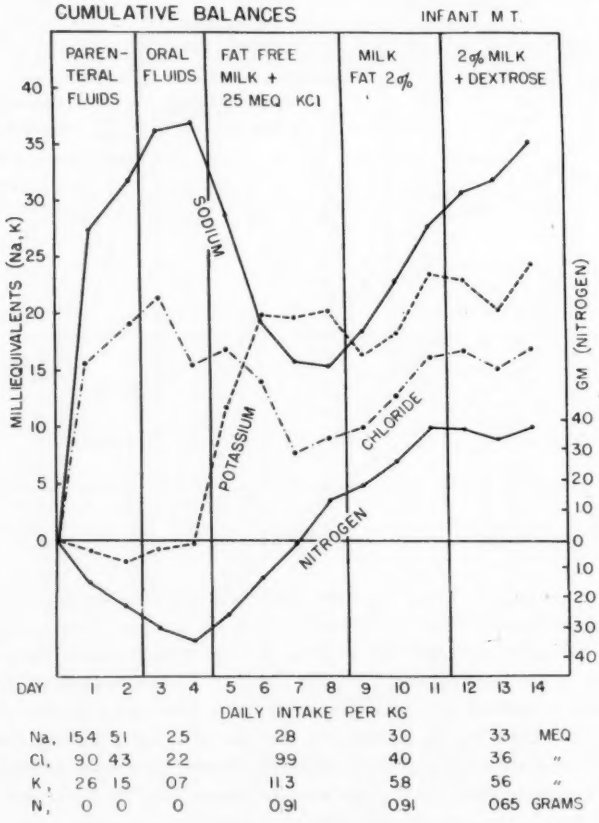


CHART 3

tains another sodium salt, which did not form part of the normal composition of the blood, or at any rate not in so large a proportion. A foreign constituent or an excess of a normal constituent, i.e., sodium carbonate, has arisen in the blood. But the kidneys possess the function of maintaining the same composition of the blood, and of thus eliminating every abnormal constituent and any excess of a normal constituent. The sodium salt formed is therefore ejected by the kidneys, together with the chlorid of potassium, and the blood becomes poorer in chlorin and sodium. Common salt is therefore withdrawn from the organism by the ingestion of potassium salts. This loss can only be made up from without, and this explains the fact that animals which live on a diet rich in potassium have a longing for salt."

This reminds us of our large debt to Arrhenius for permitting us to study the organization of body fluids on the basis of separately controlled concentrations of ions, which greatly simplifies our task. But there seems to be plenty of complexity left.

Acknowledgment

The author is greatly indebted to Prof. John P. Peters of the Yale Medical School for the loan of his treasured copy of Carl Schmidt's book.

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NEWS AND ANNOUNCEMENTS

A special course in cerebral palsy, limited to physicians only, will be given at the Cook County Graduate School of Medicine, from June 15th through June 26, 1953.

Enrollment in the course is limited, and all applications should be sent directly to the Registrar of the Cook County Graduate School of Medicine.

* * *

The Department of Pediatrics, School of Medicine, University of California at Los Angeles, recently assumed control and operation of the Marion Davies Children's Clinic, Los Angeles. This Clinic is a general pediatric clinic with appropriate subdivisions devoted to the care of sick infants and children in the Southwestern United States. Until the University Hospital of the new U.C.L.A. Medical School is completed in 1954, pediatrics will be taught to the medical students at this Clinic. Applications for pediatric internship and residency are now being accepted.

* * *

The Section on Pediatrics of the American Medical Association will meet in New York City June 2-4, 1953. The first session will be a joint meeting with the Section on Roentgenology and following it, the Chairman's Address by Dr. Eugene T. McEnery. There will be a Panel Discussion on "The Precaution of Newborn Neonatal Deaths." The third session will be a joint meeting with the Section on Public Health and Preventive Medicine and the Section on Physical Medicine consisting of a Symposium on "Poliomyelitis."

* * *

The following pediatricians have been certified in the sub-specialty of Pediatric Allergy at the examination held in Boston on Feb. 25, 1953:

Walter Richard Kessler, 3975 Broadway, New York City
Abe Matheson, 30 N. Michigan Ave., Chicago
Roland Boyd Scott, Dept. of Pediatrics, Howard University, Washington, D.C.
Sheldon C. Siegel, 711 Lowry Med. Arts Bldg., St. Paul, Minn.
Samuel Untracht, 50 E. 78th St., New York City
Ross R. Weller, 536 W. Wisconsin Ave., Milwaukee